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The effect of duration of therapy for treatment of *Staphylococcus aureus* blood stream infection: an application of cloning to deal with immortal-time bias in an analysis of data from a cohort study (BSI-FOO)

Rebecca N. Evans [1]*, Jessica Harris[1], Chris A. Rogers[1] and Alasdair P. Macgowan[2]

[1]*Bristol Trials Centre, Bristol Medical School, University of Bristol, 1–5 Whiteladies Road, Clifton, BS8 1NU, Bristol, UK;* [2]*Bristol Centre for Antimicrobial Research & Evaluation (BCARE), Infection Sciences, Pathology, North Bristol NHS Trust, Bristol, UK*

*Corresponding author. E-mail: becci.evans@bristol.ac.uk

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Objective: To estimate the effect of treatment duration on in-hospital mortality in patients with *Staphylococcus aureus* blood stream infection and demonstrate the biases that can arise when immortal-time bias is ignored.

Exposure: We compared three treatment strategies: short therapy (<10 days), intermediate (10–18 days) and long (>18 days).

Main outcome measures: Twenty-eight-day all-cause in-hospital mortality.

Methods: Using data from the BSI-FOO study, we implemented an approach proposed by Hernán to overcome confounding and immortal-time biases. The first stage is to clone all participants, so that each participant is assigned to each treatment strategy. Second, observations are censored when their data becomes inconsistent with their assigned strategy. Finally, inverse-probability weights are applied to adjust for potential selection. We compared our results to a naïve approach where immortal-time bias is ignored.

Results: Of the 1903 participants in BSI-FOO, 587 were eligible and included in the analysis. After cloning, the weighted estimates of hazard ratio of mortality for short versus long therapy was 1.74 (95% CI 1.36, 2.24) and for intermediate versus long therapy was 1.09 (0.98, 1.22). In the naïve approach, the hazard ratios with reference to the long therapy group are 37.4 (95% CI 18.9 to 74.4) in the short therapy group and 4.1 (95% CI 1.9 to 8.9) in the intermediate therapy group.

Conclusions: Our findings suggest that duration of therapy >18 days is beneficial with respect to 28-day in-hospital mortality, however, there remains uncertainty around the efficacy of reducing duration of treatment to 10–18 days.

Introduction

Staphylococcus aureus is a common cause of bloodstream infection (BSI) in hospitals across the UK. Published guidelines suggest long-course duration, i.e. 4–6 weeks of therapy is required for treatment of complicated infections such as those related to prosthetic infections or endocarditis but this can be reduced to 2 weeks for uncomplicated infections.[1–4] However, evidence for reducing the duration is based on low-quality data and the optimal length of therapy remains controversial.[5–9] Long-course therapy has the obvious benefit of maximizing the chance of infection resolution but can lead to increased NHS costs and unnecessary antibiotic exposure. Reducing the exposure to antibiotics by shortening the duration of treatment could lower the risk of adverse effects of treatment and reduce the risk of development of antibiotic resistance that is a growing problem worldwide.[10]

To date, evidence on the use of shorter therapy is limited and has been based on observational data that are subject to confounding and bias. A survival comparison between individuals with longer and shorter treatment duration will generally be biased, as only patients who survive a long time can receive treatment for a long time, i.e. there is a period of follow-up in which the outcome cannot occur. This is known as immortal-time bias and can artificially inflate the effect of longer versus shorter treatment if not adequately addressed.

In this paper, we describe an application of the three-step procedure based on participant cloning described by Hernán[11] to estimate the causal effect of duration of therapy on mortality while

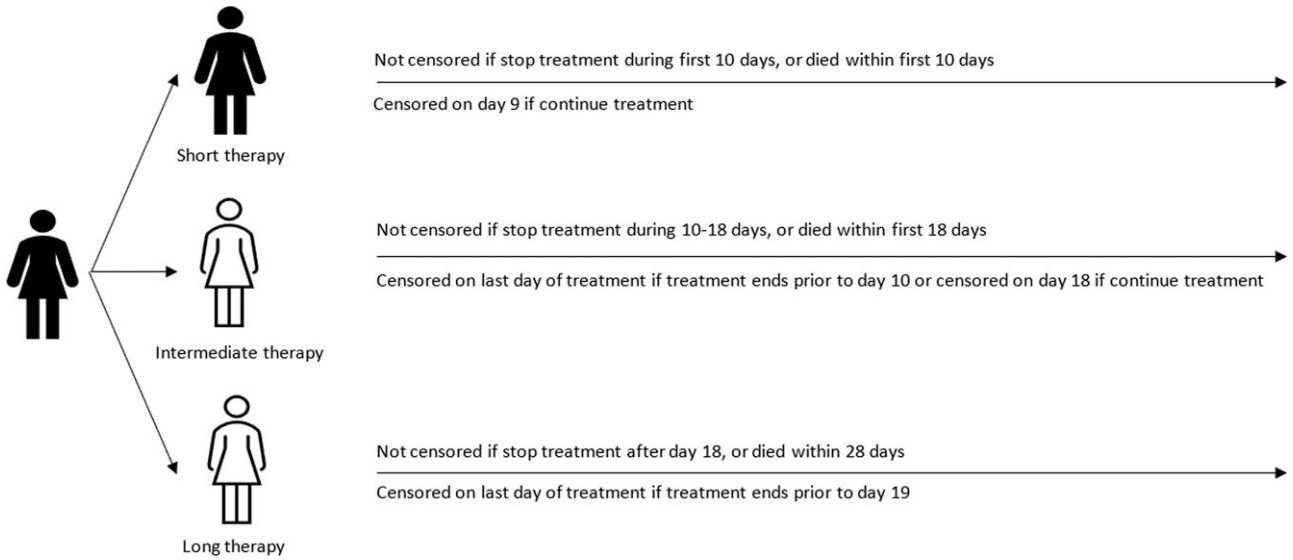

Figure 1. Illustration of patient cloning and censoring rules.

accounting for confounding and immortal-time bias and demonstrate the biases that can arise when this is ignored.

Methods

Data source

This study is a *post hoc* analysis of data from the Bloodstream Infections—Focus on Outcomes (BSI-FOO) observational study. Results of this study are published elsewhere.[12] Briefly, BSI-FOO was a multicentre cohort study of 1903 hospitalized adult patients with a BSI conducted between 2010 and 2012 with the primary aim of identifying modifiable risk factors for 28-day mortality. Information on all potentially relevant antimicrobial prescriptions were recorded from date of blood culture until day 28 or earlier discharge or death. Data included the antimicrobial name and its prescribed dose, route and frequency of administration, and the date and time of the first and last dose taken. In addition, all available local antimicrobial susceptibility results for the organisms were extracted from laboratory systems.

Study population

All BSI-FOO participants with *S. aureus* bacteraemia (SAB) were considered for inclusion, this included both MSSA and MRSA. Patients who were not in receipt of antibiotic treatment with known antimicrobial activity to MRSA/MSSA during the first 28 days post-blood culture were excluded. Polymicrobial infections and repeat episodes were also excluded.

Treatment strategies

Appropriate antibiotics were defined as antibiotics to which the pathogen showed susceptibility. The duration of appropriate antibiotic treatment, i.e. active therapy, was defined as the time interval between the first appropriate antibiotic administration and the last appropriate antibiotic administration, including any breaks between changes of treatment. Based on the distribution of duration of therapy and clinical relevance, we compared three treatment strategies:

(i) Short therapy: defined as duration of active therapy <10 days
(ii) Intermediate therapy: defined as duration of active therapy 10–18 days
(iii) Long therapy: defined as duration of active therapy >18 days.

Outcome measures

The primary outcome was 28-day all-cause in-hospital mortality from the date of initiation of appropriate therapy. We defined day 0 as the date of initiation of appropriate antibiotic treatment and censored patients at discharge or end of follow-up (28 days post-blood culture) if earlier.

Statistical analyses

Continuous data were summarized using mean and standard deviation (or median and IQR if distributions were skewed) and categorical data as numbers and percentages. Demographics, comorbidities and medical history were summarized by treatment strategy based on observed duration of therapy. Standardized mean differences were calculated to quantify imbalances in baseline characteristics by the duration of therapy group.[13] Mortality over 28 days was summarized using Kaplan–Meier survival curves and estimation of 28-day mortality by treatment strategy.

To compare the treatment strategies while eliminating immortal-time bias, we implemented the three-step procedure described by Hernán.[11] Briefly, the first stage was to clone all participants, so that each participant is assigned to each treatment strategy once. The second stage was to censor observations when an individual's data becomes inconsistent with their assigned strategy. Finally, the third stage was to apply inverse-probability weights to adjust for the potential selection bias introduced by the censoring step. We describe the steps in further detail next

In the first step, each patient was duplicated within the dataset so that each patient is represented by three observations: one assigned to their observed duration of therapy group, and the other two assigned to the remaining two groups as visualized in Figure 1.

In the second step, each participant's observational time was followed-up and censored at the point that they deviate from their assigned strategy. The events and person time that occur after the patient deviates from their assigned protocol were discarded.

Censoring patients when they deviate from their assigned strategy is a form of informative censoring and can induce selection bias.[14,15] This was corrected for in the final step using marginal structural models as

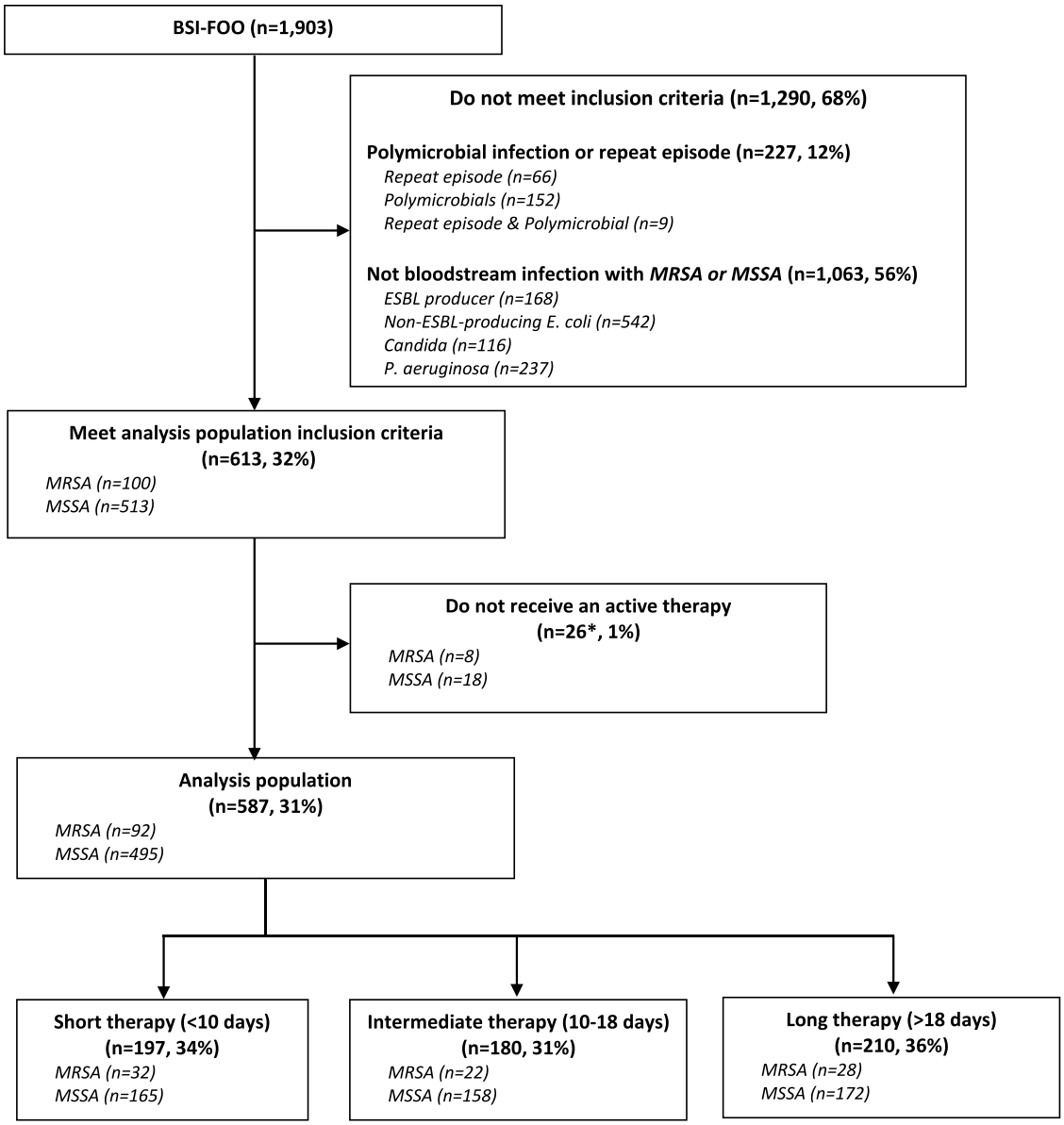

Figure 2. Flowchart. * $n=14/26$ (53.8%) died within 28 days of blood culture. $n=13$ died within 2 days of blood culture, $n=11$ survived but did not receive any treatment, $n=2$ received treatment but with therapy inactive against pathogen (one died on day 20, one survived).

introduced by Hernán *et al*. that use inverse-probability-of-censoring weights to up-weight uncensored observations to represent censored observations with similar characteristics.[16] Each participant receives a time-varying inverse probably weight estimated from a pooled logistic regression model with censoring (not being censored) as the outcome and baseline and post-baseline factors that are predictive of the censoring mechanism, i.e. variables that predict adherence to the assigned treatment duration strategy. These were specified *a priori* and included neutrophil count at baseline and maximum daily temperature measurement considered as a time-varying confounder. The denominator of the weight is calculated as the probability of remaining uncensored at time k, given that the patient has remained uncensored up to time k, their treatment on day k and their covariate history up to day k. The numerator of the weight is added to help stabilize the weights and is calculated in the same manner including only the baseline variables.

Finally, we fitted a weighted pooled logistic regression model, regressing mortality on cloned duration of treatment group weighted using the weights calculated as before. We included cubic splines of follow-up (knots at 10%, 25%, 50%, 75% and 90% percentiles) within the pooled logistic regression to mirror the underlying mortality risk. We used non-parametric bootstrapping with 500 samples to compute the 95% confidence intervals. Missing temperature measurements were imputed using last observation carried forward and baseline neutrophil count was imputed with age- and sex-adjusted averages as this was collected at one time point only.

We performed two subgroup analyses: (i) by complicated SAB and (ii) by MRSA/MSSA. We classified infection episodes as complicated when any of the following were present: persistent fever at 72 hours, presence of prosthesis and/or cardiovascular system source of infection. If all were absent then episodes were classified as non-complicated.

Table 1. Baseline characteristics, by observed duration of therapy

	Short therapy (<10 days) (*n* = 197)	Intermediate therapy (10–18 days) (*n* = 180)	Long therapy (19 + days) (*n* = 210)	SMD (I–S)	SMD (L–S)	SMD (L–I)	Overall (*n* = 587)
Patient measures							
Age	67.0 (45.0, 77.0)	66.0 (51.0, 76.0)	66.0 (48.0, 78.0)	0.07	0.03	0.03	66.0 (49.0, 77.0)
Male	120/197 (60.9%)	123/180 (68.3%)	135/210 (64.3%)	0.16	0.07	0.09	378/587 (64.4%)
Body mass index[a]	26.1 (5.9)	26.1 (6.0)	26.2 (6.5)	0.01	0.01	0.02	26.1 (6.2)
Patient medical history							
Chemotherapy in month before date 0	29/197 (14.7%)	18/180 (10.0%)	22/210 (10.5%)	0.14	0.13	0.02	69/587 (11.8%)
Any tumour within last 5 years	58/197 (29.4%)	52/180 (28.9%)	50/210 (23.8%)	0.01	0.13	0.12	160/587 (27.3%)
Surgery requiring overnight stay within 7 days before date 0	17/197 (8.6%)	22/180 (12.2%)	12/210 (5.7%)	0.12	0.11	0.23	51/587 (8.7%)
Renal support within 7 days before date 0	19/197 (9.6%)	21/180 (11.7%)	16/210 (7.6%)	0.07	0.07	0.14	56/587 (9.5%)
Myocardial infarction within 7 days before date 0	25/197 (12.7%)	24/180 (13.3%)	17/210 (8.1%)	0.02	0.15	0.17	66/587 (11.2%)
Infection severity measures							
Temperature (°C) at time 0[b]	38.2 (37.5, 38.9)	38.0 (37.2, 38.6)	38.2 (37.3, 38.8)	0.02	0.05	0.08	38.1 (37.3, 38.8)
eGFR (mL/min/1.73 m^2)[c]	78.0 (38.0, 91.0)	69.0 (36.0, 90.0)	69.5 (34.0, 90.0)	0.11	0.09	0.02	72.0 (36.0, 90.0)
Neutrophil count at day 0 or closest ($\times 10^9$/L)[d]	8.6 (4.9, 12.8)	8.8 (5.5, 12.8)	10.0 (6.9, 14.0)	0.07	0.17	0.10	9.2 (5.8, 13.3)
Systolic BP at day 0 or closest (mmHg)[e]	124.4 (27.9)	126.6 (26.9)	125.1 (25.0)	0.08	0.03	0.06	125.3 (26.5)
On IV fluids at day 0	66/197 (33.5%)	56/180 (31.1%)	59/210 (28.1%)	0.05	0.12	0.07	181/587 (30.8%)
On ventilation at day 0	20/197 (10.2%)	7/178 (3.9%)	17/209 (8.1%)	0.24	0.07	0.18	44/584 (7.5%)
On vasopressor drugs at day 0	18/197 (9.1%)	6/180 (3.3%)	8/210 (3.8%)	0.24	0.22	0.03	32/587 (5.5%)
Systemic corticosteroids in last 24 hours	30/197 (15.2%)	19/180 (10.6%)	16/210 (7.6%)	0.14	0.24	0.10	65/587 (11.1%)
EWS score nearest to day 0[f]	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.5 (1.0, 5.0)	0.16	0.00	0.17	2.0 (1.0, 4.0)
Patient comorbidities at date 0							
Congestive heart failure	31/197 (15.7%)	26/180 (14.4%)	32/210 (15.2%)	0.04	0.01	0.02	89/587 (15.2%)
Peripheral vascular disease	19/197 (9.6%)	20/180 (11.1%)	17/210 (8.1%)	0.05	0.05	0.10	56/587 (9.5%)
Cerebrovascular disease	42/197 (21.3%)	30/180 (16.7%)	27/210 (12.9%)	0.12	0.23	0.11	99/587 (16.9%)
Dementia	17/197 (8.6%)	8/180 (4.4%)	12/210 (5.7%)	0.17	0.11	0.06	37/587 (6.3%)
COPD	23/197 (11.7%)	17/180 (9.4%)	24/210 (11.4%)	0.07	0.01	0.06	64/587 (10.9%)
Connective tissue disease	13/197 (6.6%)	19/180 (10.6%)	20/210 (9.5%)	0.14	0.11	0.03	52/587 (8.9%)
Peptic ulcer disease	13/197 (6.6%)	15/180 (8.3%)	10/210 (4.8%)	0.07	0.08	0.14	38/587 (6.5%)
Ascites	16/197 (8.1%)	9/180 (5.0%)	10/210 (4.8%)	0.13	0.14	0.01	35/587 (6.0%)
Diabetes:							
None	147/197 (74.6%)	141/180 (78.3%)	169/210 (80.5%)	0.13	0.19	0.06	457/587 (77.9%)
Without organ damage	40/197 (20.3%)	28/180 (15.6%)	28/210 (13.3%)				96/587 (16.4%)
With organ damage	10/197 (5.1%)	11/180 (6.1%)	13/210 (6.2%)				34/587 (5.8%)
Child–Pugh score[g]	7.0 (6.0, 8.0)	6.0 (6.0, 7.0)	7.0 (6.0, 7.0)	0.38	0.28	0.15	7.0 (6.0, 8.0)
Charlson score[h]	3.0 (1.0, 4.0)	3.0 (1.0, 5.0)	2.0 (1.0, 4.0)	0.02	0.15	0.12	3.0 (1.0, 4.0)
Abscess at time 0	12/197 (6.1%)	21/180 (11.7%)	33/210 (15.7%)	0.20	0.31	0.12	66/587 (11.2%)
Source of infection							
Bone and joint	3/197 (1.5%)	19/180 (10.6%)	39/210 (18.6%)	0.52	0.85	0.48	61/587 (10.4%)
Cardiovascular system	6/197 (3.0%)	5/180 (2.8%)	18/210 (8.6%)				29/587 (4.9%)
Central nervous system	2/197 (1.0%)	1/180 (0.6%)	6/210 (2.9%)				9/587 (1.5%)
Line infection—central venous line	24/197 (12.2%)	25/180 (13.9%)	28/210 (13.3%)				77/587 (13.1%)
Line infection—peripheral venous line	8/197 (4.1%)	9/180 (5.0%)	6/210 (2.9%)				23/587 (3.9%)
Lower respiratory tract	14/197 (7.1%)	15/180 (8.3%)	10/210 (4.8%)				39/587 (6.6%)
Skin and soft tissue	38/197 (19.3%)	26/180 (14.4%)	23/210 (11.0%)				87/587 (14.8%)
Surgical site infection	3/197 (1.5%)	7/180 (3.9%)	14/210 (6.7%)				24/587 (4.1%)
Urinary tract infection	9/197 (4.6%)	11/180 (6.1%)	9/210 (4.3%)				29/587 (4.9%)

Continued

Table 1. *Continued*

	Short therapy (<10 days) (*n* = 197)	Intermediate therapy (10–18 days) (*n* = 180)	Long therapy (19 + days) (*n* = 210)	SMD (I–S)	SMD (L–S)	SMD (L–I)	Overall (*n* = 587)
Site uncertain	83/197 (42.1%)	51/180 (28.3%)	47/210 (22.4%)				181/587 (30.8%)
Other	7/197 (3.6%)	11/180 (6.1%)	10/210 (4.8%)				28/587 (4.8%)
Lines and catheters							
Central line present at time 0	57/197 (28.9%)	45/180 (25.0%)	50/210 (23.8%)	0.09	0.12	0.03	152/587 (25.9%)
Peripheral line present at time 0	104/197 (52.8%)	95/180 (52.8%)	96/210 (45.7%)	0.00	0.14	0.14	295/587 (50.3%)
Urinary catheter present at time 0	67/197 (34.0%)	45/180 (25.0%)	57/210 (27.1%)	0.20	0.15	0.05	169/587 (28.8%)
Organizational factors							
Centre:							
A	26/197 (13.2%)	30/180 (16.7%)	41/210 (19.5%)	0.25	0.18	0.21	97/587 (16.5%)
B	41/197 (20.8%)	27/180 (15.0%)	39/210 (18.6%)				107/587 (18.2%)
C	70/197 (35.5%)	58/180 (32.2%)	67/210 (31.9%)				195/587 (33.2%)
D	17/197 (8.6%)	26/180 (14.4%)	18/210 (8.6%)				61/587 (10.4%)
E	43/197 (21.8%)	39/180 (21.7%)	45/210 (21.4%)				127/587 (21.6%)
Ward specialty on day 0:							
Medicine	109/193 (56.5%)	100/177 (56.5%)	102/209 (48.8%)	0.27	0.36	0.16	311/579 (53.7%)
Critical care	28/193 (14.5%)	21/177 (11.9%)	26/209 (12.4%)				75/579 (13.0%)
Surgery	43/193 (22.3%)	52/177 (29.4%)	76/209 (36.4%)				171/579 (29.5%)
Other	13/193 (6.7%)	4/177 (2.3%)	5/209 (2.4%)				22/579 (3.8%)
Treatment							
Time to receipt of active therapy (days)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.09	0.22	0.07	0.0 (0.0, 1.0)

Abbreviations: eGFR = Estimated glomerular filtration rate, BP = Blood pressure, EWS = Early warning score, IV = Intravenous
Missing data (Short therapy, Intermediate therapy, Long therapy):
[a]Data missing for 301 patients (117, 87, 97).
[b]Data missing for nine patients (4, 3, 2).
[c]Data missing for 44 patients (18, 12, 14).
[d]Data missing for 54 patients (20, 14, 20).
[e]Data missing for 93 patients (35, 27, 31).
[f]Data missing for 278 patients (99, 89, 90).
[g]Data missing for 379 patients (139, 115, 125).
[h]Data missing for 128 patients (47, 39, 42).

A sensitivity analysis to explore the impact of censoring at hospital discharge was performed by including follow-up and events after hospital discharge. Daily temperature measurements were not recorded post-discharge so normal temperature (37°C) was assumed for this period. We also performed a sensitivity analysis adjusting for baseline factors: source of infection, age, eGFR, systolic BP, on IV fluids, on ventilation, on vasopressor and systemic corticosteroids in the last 24 hours.

We contrasted the results using this approach with the results obtained from a naïve analysis in an unadjusted Cox regression model with observed duration of therapy as exposure where confounding and immortal-time bias are ignored and in a confounder-adjusted model where immortal-time bias is ignored. We also contrast the results with an alternative approach using time-varying treatment variables in a weighted pooled logistic regression model where the treatment duration group is updated daily to be consistent with the treatment duration received up until that day, accounting for both confounding and immortal-time biases. In this approach, the bias is reduced because at each time point patients are assigned to the treatment duration group consistent with their data up to that time point (not looking forward in time) i.e. all patients are assigned to the short therapy group for the period up to day 10, at which point those who continue treatment will be updated and assigned intermediate therapy and those who do not will continue to be assigned short therapy.

Long therapy was used as the reference category for all analyses as this category most closely represents current guidelines. All analyses were performed in Stata v.16.1 (StataCorp, LP, College Station, TX, USA).

Results

Of the 1903 participants in the BSI-FOO study, 587 (30.8%, 92 MRSA and 495 MSSA) met the eligibility criteria and were included in the analysis (Figure 2). On the basis of the observed duration of therapy, i.e. before cloning, 33.6% (197/587) received active treatment for <10 days, 30.7% (180/687) received active treatment for 10–18 days and 35.8% (210/587) received active treatment for >18 days. The most common therapies prescribed for MRSA were Vancomycin (77.2%) followed by Rifampicin (28.3%). In patients with MSSA, the most commonly prescribed treatment was Flucloxacillin (78.0%) followed by Piperacillin-tazobactam (39.0%). See Supplementary Tables S1–S3 (available as Supplementary

Table 2. Primary outcome: 28-day mortality

	Short therapy	Intermediate therapy	Long therapy
Naïve approach			
Proportion died	82/197 (41.6%)	21/180 (11.7%)	10/210 (4.8%)
Hazard ratio (95% CI)	37.45 (18.86, 74.37)	4.12 (1.92, 8.87)	Ref.
Adjusted hazard ratio[a] (95% CI)	42.57 (17.42, 104.49)	4.81 (1.85, 12.49)	Ref.
Time-updated covariates			
Hazard ratio (95% CI)[b]	7.82 (2.10, 29.17)	1.37 (0.38, 4.97)	Ref.
Three-step procedure			
Hazard ratio (95% CI)[b]	1.74 (1.36, 2.24)	1.09 (0.98, 1.22)	Ref.
Sensitivity analysis 1[c]			
Hazard ratio (95% CI)[b]	1.36 (1.14, 1.64)	0.97 (0.88, 1.08)	Ref.
Sensitivity analysis 1[d]			
Hazard ratio (95% CI)[b]	1.63 (1.25, 2.14)	1.12 (0.99, 1.27)	Ref.
Subgroup analysis 2[e]			
Complicated ($n=140$)	3.04 (1.32, 7.00)	1.25 (0.87, 1.79)	Ref.
Non-complicated ($n=425$)	1.70 (1.26, 2.29)	1.08 (0.95, 1.22)	Ref.
Subgroup analysis 2[f]			
MRSA ($n=92$)	2.92 (1.45, 5.88)	1.07 (0.92, 1.25)	Ref.
MSSA ($n=495$)	1.54 (1.19, 2.00)	1.10 (0.97, 1.24)	Ref.

Notes:
[a]Adjusted for: age, source of infection, neutrophil count on day of blood culture, eGFR, systolic BP, on IV fluids, on ventilation, on vasopressor and systemic corticosteroids.
[b]Hazard ratios estimated from a weighted pooled logistic regression model, using inverse probability of censoring weights calculated using baseline neutrophil count and daily temperature measurements.
[c]Including follow-up and deaths after hospital discharge. Normal temperature (37°C) was assumed after hospital discharge.
[d]Additionally adjusted for age, source of infection, eGFR, systolic BP, on IV fluids, on ventilation, on vasopressor and systemic corticosteroids in the estimation of weights.
[e]Subgroup analysis 1: By complicated/non-complicated SAB where complicated is defined when any of the following were present: persistent fever at 72 hours, presence of prosthesis, cardiovascular system source of infection. Data missing for 22 patients. *P* value for interaction = 0.43.
[f]Subgroup analysis 2: By MRSA/MSSA. *P* value for interaction = 0.12.

data at *JAC* Online) for frequencies of prescribed treatments by duration of therapy group, MRSA/MSSA and complication of infection respectively. Table 1 summarizes the distribution of baseline characteristics, by observed duration of therapy. The median age was 66.0 years (IQR 49.0, 77.0) and 64.4% (378/387) were male. Baseline characteristics were broadly similar across the groups, however, there were some differences in some of the clinical measures. eGFR was on average higher indicating better kidney function in patients in the short therapy group compared to the intermediate and long therapy groups [median 78.0 versus 69.0 versus 69.5, standardized mean difference (SMD) = 0.11 (Intermediate versus Short), 0.09 (Long versus Short) and 0.02 (Long versus Intermediate), respectively]. Source of infection was more commonly skin and soft tissue (19.3% versus 14.4% versus 11.0%) and site uncertain (42.1% versus 28.3% versus 22.4%) and less commonly bone and joint (1.5% versus, 10.6% versus 18.6%) in patients in the short therapy group compared to the intermediate and long therapy (SMD Intermediate versus Short = 0.52, Long versus short = 0.85 and Long versus Intermediate = 0.48). A larger proportion were on vasopressor drugs on day 0 (9.1% versus 3.3% versus 3.8%) and systemic corticosteroids (15.2% versus 10.6% versus 7.6%). However, this difference is maybe a reflection of fact that sicker patients are more likely to die early and therefore more likely to be in the short therapy group as they did not survive long enough to receive longer duration of therapy. Therefore, these descriptive summaries are subject to immortal-time bias as described previously. Once cloned, all participants were represented by a clone in the short, intermediate and long therapy group, therefore baseline characteristics of the three groups were perfectly balanced at time zero i.e. before censoring.

In the overall cohort, a total of 113/587 (19.3%) patients died in hospital within 28 days.

Three-step procedure

After cloning, the weighted estimates of the hazard ratios of all-cause mortality for short therapy versus long therapy was 1.74 (95% CI 1.36 to 2.24) and 1.09 (95% CI 0.98 to 1.22) for intermediate versus long (Table 2). In subgroup analyses, there was no evidence to suggest that this effect differed by complication of infection (*P* value for interaction = 0.43) or by methicillin-susceptibility (*P* value for interaction 0.12), see Table 2. The sensitivity analysis including time and events after hospital discharge showed similar but weaker associations, possibly explained by deaths after discharge unlikely to be attributed to infection/treatment and therefore biasing the results towards null (Table 2). The sensitivity analysis adjusting for additional baseline variables provided results consistent with the primary analysis (Table 2).

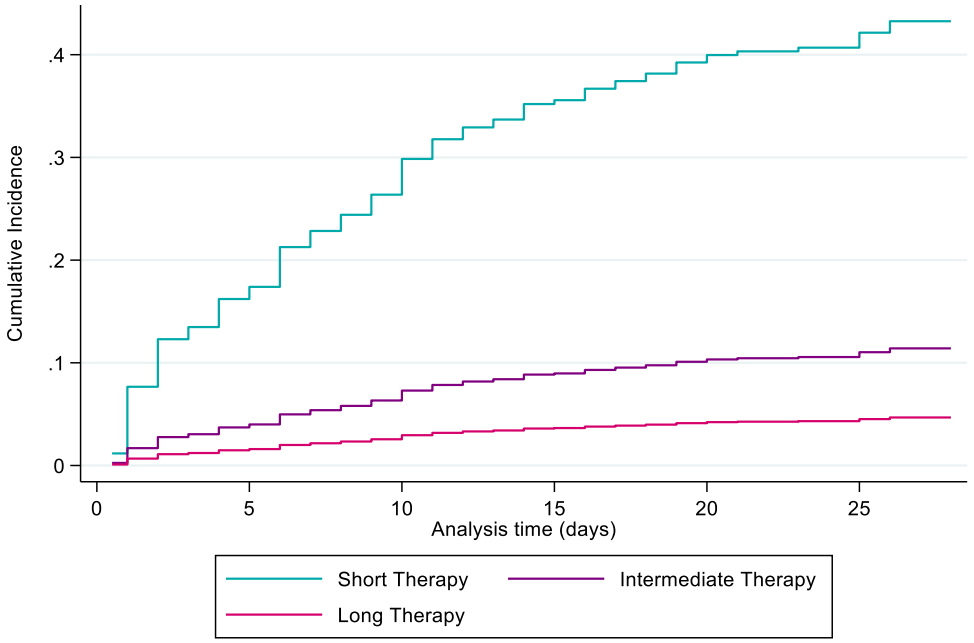

Figure 3. Cumulative incidence functions for time to death, by duration of therapy group. Note: Group 1 = Short therapy, Group 2 = Intermediate therapy, Group 3 = Long therapy. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Naïve approach

Unsurprisingly, in an unadjusted analysis where treatment strategy was based on the observed exposure status, before cloning, the crude 28-day in-hospital mortality was highest in the short therapy group (41.6%) followed by intermediate therapy (11.7%) and lowest in those in the long therapy group (4.8%), see Table 2 and Figure 3. The estimated unadjusted hazard ratios with reference to the long therapy group are 37.4 (95% CI 18.9 to 74.4) in the short therapy group and 4.1 (95% CI 1.9 to 8.9) in the intermediate therapy group.

Time-updating covariates

When applying time-updating covariates, the unweighted Kaplan–Meier estimate of 28-day in-hospital mortality decreased to 57.7% (95% CI 41.3 to 75.0) in the short therapy group, 10.2% (95% CI 5.3 to 19.0) in the intermediate group and 5.2% (95% CI 2.7 to 9.8) in the long therapy group. After weighting, with reference to the long therapy group, the estimated hazard ratios are 7.82 (95% CI 2.10 to 29.17) in the short therapy group and 1.37 (95% CI 0.38 to 4.97) in the intermediate therapy group, showing evidence of a benefit of longer therapy versus short therapy.

Discussion

There is limited trial evidence to guide optimal duration of therapy for the treatment of BSI. Results of a clinical trial in *Escherichia coli* were recently published, although trial evidence is lacking in SAB.[17] Previous observational studies examining duration of therapy have been criticized for the presence of immortal-time bias.[5–8] We implemented a novel approach to address the bias introduced by confounding and immortal time and our estimates suggest longer treatment (>18 days) is beneficial compared to <10 days of treatment, however, uncertainty remains around the effect of a duration of 10–18 days with our estimates compatible with a range of 2% decrease to 22% increase in hazard of mortality compared to long course (>18 days).

A recent single centre cohort study reported a 68% reduction in mortality in patients treated for >14 days compared to ≤14 days (95% CI 0.16 to 0.64) in patients with complicated SAB and no difference in mortality in patients with uncomplicated SAB (adjusted HR 0.85, 95% CI 0.41 to 1.78).[5] Similarly, we found a reduction in effect size in the subgroup of non-complicated infections, however, the number of events within our subgroups was small so the power of this subgroup analysis is limited. Abbas *et al.* defined complicated infections as any of: endocarditis, implant, duration of SAB >2 days, fever >3 days, however, we were unable to include duration of SAB or endocarditis in our definition as this data was not collected in BSI-FOO. In the cohort study reported by Abbas *et al.*, patients who died within 14 days and therefore not given the chance to receive 14 days of therapy were excluded from the analysis to overcome immortal-time bias. However, this may have introduced selection bias in their estimates as the sicker patients or those with severe infections may be excluded.

We attempted to eliminate immortal-time bias by implementing a novel approach involving 'cloning' and 'censoring' that does not require exclusions based on survival time. We contrasted the estimates from this approach with estimates from a Cox regression model where confounding and immortal-time bias are ignored (naïve approach) and also from a Cox regression model with time-updated treatment covariates. The effect size was largest in the naïve approach: however, these estimates are likely to be extremely biased. The effect sizes were reduced when using time-updated covariates, but these remained higher

than the estimates using the cloning approach. This may be explained by early deaths contributing to all three groups when using the cloning approach but would only contribute to the short therapy group using the updated covariate approach.

There are several limitations to our study. First, the analysis approach did not account for hospital discharge as a competing risk. It was not possible to perform a competing risk model while allowing for the time-varying weights. We therefore performed a pooled logistic model that allowed for time-varying weights and censored patients at hospital discharge. This may lead to an overestimation of the effect of treatment duration, however, a sensitivity analysis including follow-up and deaths after discharge showed similar associations. Second, there are many reasons why patients may cease treatment at a particular time; it may be according to a prespecified treatment strategy, or they may cease or change treatment due to side effects or if their condition has improved so that no further treatment is necessary. The retrospective nature of the study meant that information on reason for continuing/discontinuing treatment was not captured. We accounted for the artificial censoring using inverse-probability weights that included neutrophil count at baseline and daily temperature measurements, however, it is not possible to rule out unmeasured confounding as factors such as C-Reactive protein or procalcitonin measurement that may be associated with clinicians' decisions in discontinuing treatment and information on these was not collected in BSI-FOO. In addition, the administration of antipyretic agents may influence patients' temperatures, however, it was not possible to adjust for this as information on the administration of antipyretic agents were not collected in BSI-FOO. We also did not consider dosing or other treatment strategies such as surgical removal of the source as these were beyond the scope of this analysis, however, they are important factors for future research. The use of an observational dataset defined for a different study protocol also limited the definition of complicated infection that could be applied for the subgroup analysis. Follow-up blood cultures were not recorded in the dataset, so it was not possible to identify positive blood cultures after the initial blood culture. Endocarditis was also not recorded so we used cardiovascular system source of infection as a surrogate. Finally, the research is limited to a single data source from a research programme that was conducted over 10 years ago.

Applying the three-step procedure as described by Hernán resulted in less biased estimates of the effect of duration of treatment, however, the data used in these analyses were collected to answer a different research question, meant that some data items relevant to this research were not collected. This includes the development of secondary sources of infection that may prolong treatment administration and side effects of treatment that may shorten treatment. These are important to consider in the design of future studies designed to answer this research question.

We implemented a novel approach to address the bias introduced by confounding and immortal time and our estimates suggest longer treatment (>18 days) is beneficial compared to <10 days of treatment; however, the effect of a duration of 10–18 days is less certain with our estimates compatible with a range of 2% benefit to 22% harm in survival compared to >18 days of treatment. To date, there are no published randomised controlled trials evaluating duration of treatment for SAB, however, there is currently a trial in recruitment comparing the efficacy of 7 and 14 days of antibiotic treatment in uncomplicated *S. aureus* bacteraemia.[18] Until the results of this trial are available, or an observational analysis designed to answer this question with an appropriate analytical approach to deal with immortal-time bias such as the three-step procedure applied in this setting has been performed, we do not recommend duration of therapy to be <10 days for SAB. Treatment duration 10–18 days may be adequate for uncomplicated infections, however, reducing duration of therapy in clinical practice should be adopted with caution until sufficiently powered studies are published allowing more accurate and precise estimation of the effect.

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Transparency declarations

There are no conflicts of interest to declare.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Availability of data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplementary data

Tables S1–S3 are available as Supplementary data at *JAC* online.

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