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Comparative effectiveness of β-lactams for empirical treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia: a prospective cohort study

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Objectives: Standard once-daily dosing of ceftriaxone may not lead to adequate antibiotic exposure in all cases of Staphylococcus aureus bacteraemia (SAB). Therefore, we compared clinical effectiveness of empirical antibiotic treatment with flucloxacillin, cefuroxime and ceftriaxone in adult patients with MSSA bacteraemia

Methods: We analysed data from the Improved Diagnostic Strategies in *Staphylococcus aureus* bacteraemia (IDISA) study, a multicentre prospective cohort study of adult patients with MSSA bacteraemia. Duration of bacteraemia and 30 day SAB-related mortality were compared between the three groups using multivariable mixed-effects Cox regression analyses.

Results: In total, 268 patients with MSSA bacteraemia were included in the analyses. Median duration of empirical antibiotic therapy was 3 (IQR 2–3) days in the total study population. Median duration of bacteraemia was 1.0 (IQR 1.0–3.0) day in the flucloxacillin, cefuroxime and ceftriaxone groups. In multivariable analyses, neither ceftriaxone nor cefuroxime was associated with increased duration of bacteraemia compared with flucloxacillin (HR 1.08, 95% CI 0.73–1.60 and HR 1.22, 95% CI 0.88–1.71). In multivariable analysis, neither cefuroxime nor ceftriaxone was associated with higher 30 day SAB-related mortality compared with flucloxacillin [subdistribution HR (sHR) 1.37, 95% CI 0.42–4.52 and sHR 1.93, 95% CI 0.67–5.60].

Conclusions: In this study, we could not demonstrate a difference in duration of bacteraemia and 30 day SAB-related mortality between patients with SAB empirically treated with flucloxacillin, cefuroxime or ceftriaxone. Since sample size was limited, it is possible the study was underpowered to find a clinically relevant effect.

Introduction

Delayed initiation of adequate antibiotic therapy is associated with increased mortality in *Staphylococcus aureus* bacteraemia (SAB).[1] However, until blood culture results become available, patients with MSSA bacteraemia frequently receive empirical antibiotic treatment targeting severe infection or sepsis. In a setting with low MRSA prevalence, broader-spectrum ß-lactams, including cefuroxime and ceftriaxone, are often used for such empirical treatment. Based on pharmacokinetic/pharmacodynamic analyses

and one clinical study, there are concerns that, in contrast to cefuroxime therapy, standard once-daily dosing of ceftriaxone does not lead to adequate antibiotic exposure in SAB and therefore results in suboptimal patient outcomes.[2–4] Cefuroxime and ceftriaxone have never been directly compared as empirical treatment of MSSA bacteraemia. Therefore, in this study we aimed to determine the effectiveness of empirical antibiotic treatment with flucloxacillin, cefuroxime and ceftriaxone in adult patients with subsequent microbiologically proven MSSA bacteraemia.

Methods

Study design and study population

We analysed data from the Improved Diagnostic Strategies in *Staphylococcus aureus* bacteraemia (IDISA) study, a multicentre, prospective cohort study of patients with SAB (Netherlands Trial Register NTR6669).[5,6] An extensive description of the IDISA study can be found elsewhere.[6] For the current study, we included patients with MSSA bacteraemia who received flucloxacillin, cefuroxime or ceftriaxone as empirical therapy. Empirical therapy was defined as administration of these agents before results of blood cultures became available. Patients were excluded if they received a combination of two or more of these three agents as empirical therapy, but combination therapy with another agent, e.g. an aminoglycoside, was allowed. Other exclusion criteria were initiation of treatment after the date of first negative blood culture and not performing a follow-up blood culture within 7 days. There was no restriction with regard to the dose of each empirical antibiotic agent. The study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam (METC2017_094).

Outcomes

The primary outcome of this study was duration of bacteraemia, counted in days from start of empirical flucloxacillin, cefuroxime or ceftriaxone (Figure 1). The day of the last positive blood culture was counted as the last day of bacteraemia.[7] To investigate whether detection bias was present due to irregular sampling of blood cultures, the median number of days between the last positive and first negative blood culture was calculated for each group. As a sensitivity analysis, duration of bacteraemia was calculated as the number of days between start of empirical therapy and the midpoint in time between the last positive and the first negative blood culture in patients with a known negative blood culture. Secondary outcome was 30 day SAB-related mortality, defined as death from direct complications of the infection (e.g. septic brain haemorrhage, heart failure from endocarditis) or with active infection at the time of death, defined as persistent signs of infection, positive blood cultures, or a persistent uncontrolled focus of infection. Presence of SAB-related mortality was adjudicated based on medical record review by two independent ID physicians. If no consensus was reached, a third reviewer could be consulted.

Data collection

Demographic variables (age, sex), comorbidities (Charlson comorbidity index), clinical data [presence of severe sepsis, SAB acquisition type (community acquired, hospital acquired, healthcare associated), focus of infection, presence of implanted prosthetic material], microbiological data (timing and results of blood cultures) and treatment data (agents used for antibiotic therapy) were prospectively collected from electronic health records (EHRs).[8] Severe sepsis and SAB acquisition type were defined as described previously.[9,10] In patients with multiple infection foci, the dominant focus was reported as proposed earlier.[11] The study team assessed outcomes by telephone interview after Day 90. For patients who could not be reached by telephone, post-discharge health status was determined through contact with the patient's primary care physician, the hospital EHR, and municipal death records.

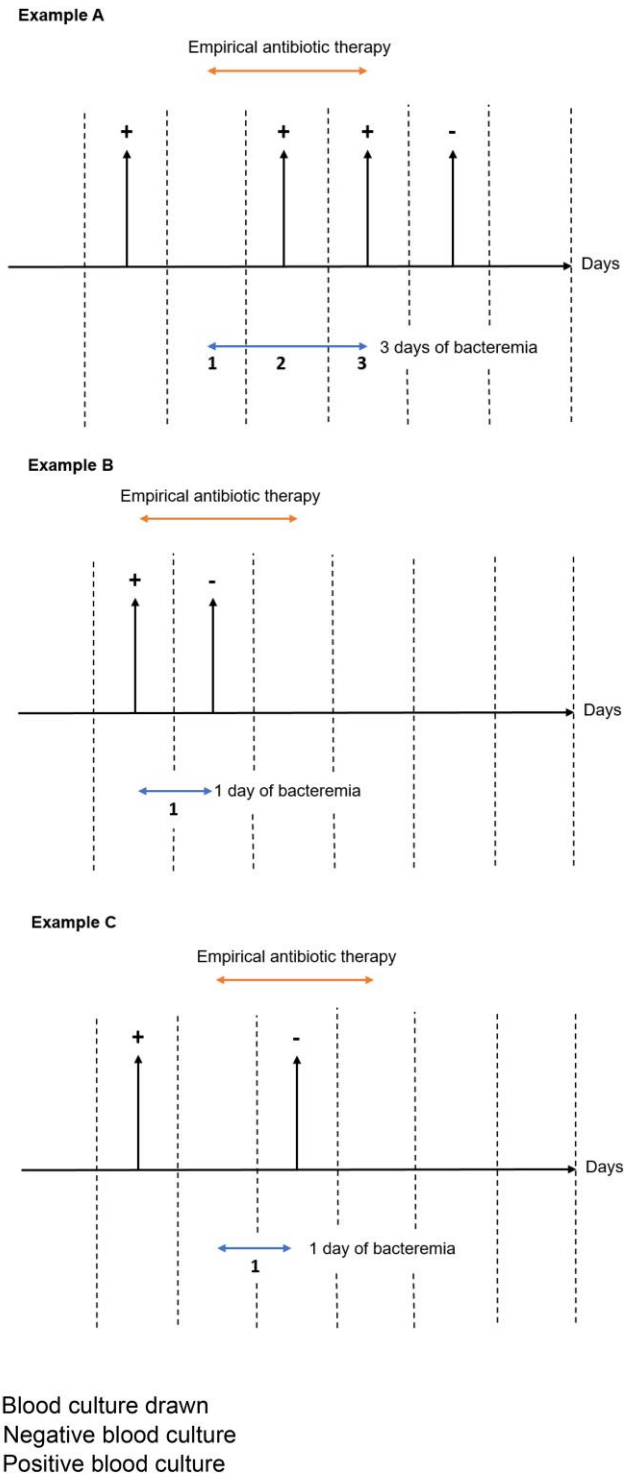

Figure 1. Examples of definition of bacteraemia duration.[7] This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

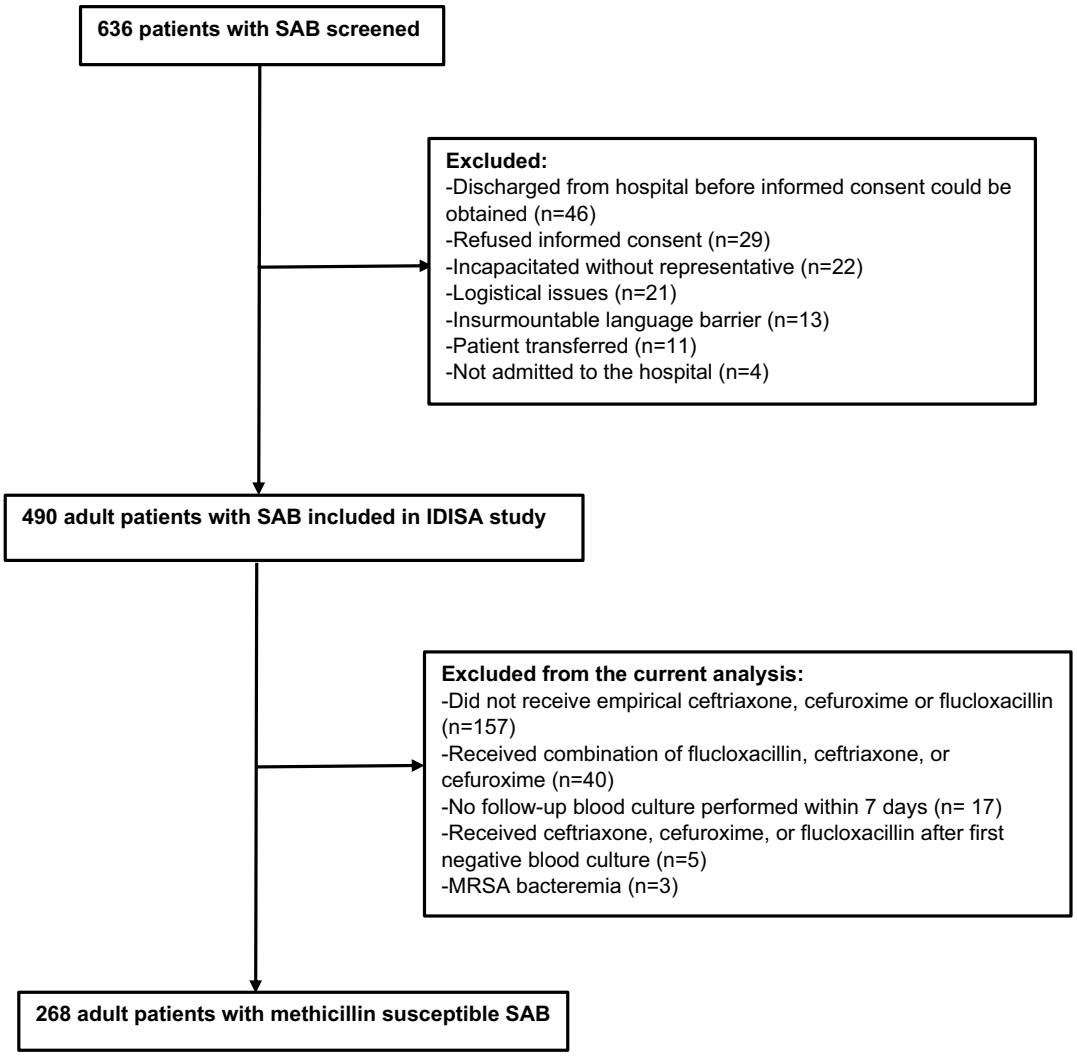

Figure 2. Flow chart of the study.

Statistical analyses

Baseline categorical patient characteristics were summarized by presenting numbers and percentages, and continuous characteristics by presenting the mean and SD or the median and IQR, as appropriate. All-cause mortality was only analysed with descriptive statistics. Kaplan–Meier estimates were plotted for time to primary and secondary outcome. Start of survival time was set at start of empirical treatment. Mixed-effects Cox regression analyses were performed with random intercepts corresponding to the hospital of admission to estimate the association between empirical agent and outcomes. For the mixed-effects model, the number of clusters was reduced from seven to five by combining different locations from the same hospital network to create clusters of comparable size. Patients without a known negative blood culture were censored on the day of the last positive blood culture in all analyses with bacteraemia duration as outcome. First, a crude mixed-effects analysis was performed for all outcomes. Second, a multivariable analysis was performed. For bacteraemia duration, adjustment was performed for age, Charlson comorbidity index, SAB acquisition (community acquired, hospital acquired, healthcare associated), presence of severe sepsis, empirical aminoglycoside use, and dominant focus of infection (Duke definite endocarditis, osteoarticular infection, central or peripheral venous catheter infection, or other focus).[12] For 30 day SAB-related mortality, adjustment was performed for all of the above variables except empirical aminoglycoside use. These variables were selected based on their association with mortality in previous studies.[1] We performed a competing risk analysis using the Fine and Gray survival regression model to estimate the subdistribution hazard ratio (sHR) for SAB-related mortality, since non-SAB related mortality is a competing event for this outcome.[13] Covariates that showed non-proportional hazards over time by visual inspection of Schoenfeld residuals were added as time-dependent covariates to the model. Linearity between continuous covariates and the log hazard rate was checked by visual inspection of Martingale residuals. There were no missing data for the variables used in this study. All analyses were performed using R version 4.0.3, and a *P* value smaller than 0.05 was considered statistically significant.

Results

Study population

Figure 2 shows the flow chart for inclusion in the study. After screening 636 patients, 490 adult patients with SAB were

Table 1. Baseline characteristics of study population

	Total study population $n=268$	Flucloxacillin $n=49$	Cefuroxime $n=65$	Ceftriaxone $n=154$
Female	91 (34)	17 (35)	19 (29)	55 (36)
Age, years, median (IQR)	67 (58–76)	64 (54–72)	68 (61–76)	68 (58–79)
Charlson comorbidity index, median (IQR)	3 (2–5)	3 (2–5)	3 (2–4)	3 (2–5)
SAB acquisition				
Community acquired	85 (32)	10 (20)	23 (35)	52 (34)
Hospital acquired	86 (32)	21 (43)	11 (17)	54 (35)
Healthcare associated	97 (36)	18 (37)	31 (48)	48 (31)
Severe sepsis	112 (42)	16 (33)	22 (34)	74 (48)
Implanted prosthetic material	113 (42)	24 (49)	31 (48)	58 (38)
Infection type				
Endocarditis	55 (21)	4 (8)	15 (23)	36 (23)
Osteoarticular infection	57 (21)	18 (37)	23 (35)	16 (10)
Pneumonia	22 (8)	2 (4)	3 (5)	17 (11)
Other focus	39 (15)	3 (6)	9 (14)	27 (18)
SSTI	18 (7)	3 (6)	6 (9)	9 (6)
CVC infection	19 (7)	2 (4)	2 (3)	15 (10)
PVC infection	36 (13)	16 (33)	3 (5)	17 (11)
Unknown focus	22 (8)	1 (2)	4 (6)	17 (11)
Antibiotic dosage used	NA	4 g/24 h: 17 (35) 6 g/24 h: 24 (49) 12 g/24 h: 8 (16)	1500 mg TID: 50 (77) 750 mg TID: 15 (23)	2 g OD: 146 (94) 2 g BID: 10 (6)
Empirical aminoglycoside	47 (18)	8 (16)	13 (20)	26 (17)
Duration of empirical therapy, days	3 (2–3)	3 (2–3)	3 (2–4)	3 (2–3)

All data are *n* (%) unless stated otherwise. SSTI, skin and soft tissue infection; CVC, central venous catheter; PVC, peripheral venous catheter; NA, not applicable; OD, once daily, BID, twice daily, TID, three times daily.

included in the IDISA study. After applying the exclusion criteria, 268 patients remained for inclusion in the current study. Prevalence of hospital-acquired bacteraemia was highest in the flucloxacillin group (Table 1). Frequency of severe sepsis was highest in the ceftriaxone group. There were large differences between the groups with regard to dominant focus of infection. Osteoarticular infection and peripheral venous catheter infection were the most common focus of infection in the flucloxacillin group, and endocarditis in the ceftriaxone group. In the ceftriaxone group, 94% of patients received ceftriaxone at 2 g once daily. The majority of patients treated with flucloxacillin received a dosage of less than 12 g/24 h. Median duration of empirical antibiotic therapy was 3 days in all groups.

Primary outcome

Median duration of bacteraemia was 1.0 day (IQR 1.0–3.0) in the flucloxacillin group, 1.0 day (IQR 1.0–3.0) in the cefuroxime group, and 1.0 day (IQR 1.0–3.0) in the ceftriaxone group. Figure S1 (available as Supplementary data at *JAC* Online) shows the Kaplan–Meier curve for bacteraemia duration per group. Table 2 shows results of crude and multivariable adjusted effects of cefuroxime and ceftriaxone on outcomes with flucloxacillin as reference group. In multivariable analyses, neither cefuroxime nor ceftriaxone was associated with increased duration of bacteraemia compared with flucloxacillin (HR 1.08, 95% CI 0.73–1.60 and HR 1.22, 95% CI 0.88–1.71). In comparison with cefuroxime, ceftriaxone was also not associated with increased duration of bacteraemia (HR 1.13, 95% CI 0.83–1.55).

Sensitivity analysis

In the total study population, 12 patients (4%) had no known negative blood culture, of whom 9 died or received palliative care before control blood cultures could be drawn. The median number of days between the last positive and first negative blood culture in patients with a known negative blood culture was 2.0 days (IQR 2.0–3.0) in the flucloxacillin group, 3.0 days (IQR 2.0–4.0) in the cefuroxime group, and 2.0 days (IQR 1.0–3.0) in the ceftriaxone group. If bacteraemia duration was calculated as the number of days between start of empirical therapy and the midpoint in time between the last positive and the first negative blood culture, median duration was 2.5 days (IQR 2.0–3.8) in the flucloxacillin group, 3.0 days (IQR 2.4–4.1) in the cefuroxime group, and 2.5 days (IQR 2.0–4.0) in the ceftriaxone group. Using this alternative calculation of the outcome in order to account for irregular sampling of blood cultures, neither cefuroxime nor ceftriaxone was associated with increased duration of bacteraemia in comparison with flucloxacillin (HR 1.01, 95% CI 0.66–1.54 and HR 1.24, 95% CI 0.86–1.79).

Secondary outcome

In the total study population 30 day all-cause mortality was 22%: 8% in the flucloxacillin, 17% in the cefuroxime, and 29%

Table 2. Association between empirical antibiotic therapy and outcomes

	Number of patients	Number of SAB-related deaths (%)	Bacteraemia duration crude HR (95% CI)	Bacteraemia duration multivariable HR (95% CI)	30 day SAB-related mortality crude sHR (95% CI)	30 day SAB-related mortality multivariable sHR (95% CI)
Flucloxacillin	49	4 (8)	reference	reference	reference	reference
Cefuroxime	65	10 (15)	1.05 (0.72–1.54)	1.08 (0.73–1.60)	2.03 (0.64–6.47)	1.37 (0.42–4.52)
Ceftriaxone	154	31 (20)	1.11 (0.80–1.54)	1.22 (0.88–1.71)	2.62 (0.93–7.43)	1.93 (0.67–5.60)

Mixed-effects Cox regression with flucloxacillin as reference. Multivariable analysis bacteraemia duration: adjusted for age, Charlson comorbidity index, SAB acquisition (community acquired, hospital acquired, healthcare associated), presence of severe sepsis, empirical aminoglycoside use, and dominant focus of infection (Duke definite endocarditis, osteoarticular infection, central or peripheral venous catheter infection, or other focus). Multivariable analysis 30 day SAB-related mortality: adjusted for all of the above variables except empirical aminoglycoside.

in the ceftriaxone group. Overall 30 day SAB-related mortality was 17%. In the flucloxacillin, cefuroxime and ceftriaxone groups, 30 day SAB-related mortality was 8%, 15% and 20%, respectively. Figure S2 shows the Kaplan–Meier curve for 30 day SAB-related mortality per group. In multivariable analyses, neither cefuroxime nor ceftriaxone was associated with higher 30 day SAB-related mortality than flucloxacillin (sHR 1.37, 95% CI 0.42–4.52 and sHR 1.93, 95% CI 0.67–5.60). In comparison with cefuroxime, ceftriaxone was not associated with increased 30 day SAB-related mortality either (sHR 1.41, 95% CI 0.67–3.00).

Discussion

In this prospective observational cohort study of 268 adult patients with MSSA bacteraemia, we could not demonstrate a difference in duration of bacteraemia or 30 day SAB-related mortality between patients empirically treated with flucloxacillin, cefuroxime or ceftriaxone.

Evidence concerning optimal empirical therapy of MSSA bacteraemia is scarce. Two recent retrospective studies compared cefuroxime with piperacillin/tazobactam and cloxacillin or cefazolin with β-lactam/β-lactamase inhibitor combinations, respectively.[14,15] In both studies, no difference in mortality was observed between treatment strategies (matched HR 0.82, 95% CI 0.47–1.46 and adjusted OR 0.53, 95% CI 0.18–1.51, respectively). Vancomycin was compared with β-lactams as empirical therapy in MSSA bacteraemia in an observational study.[16] In this study, earlier clearance of bacteraemia by a median of 1 day was reported in the β-lactam group, but no difference in mortality was observed between the groups. However, patients in the β-lactam group were treated with a wide range of antibiotic agents, making these results difficult to interpret. In another retrospective study, empirical treatment with ceftriaxone or cefotaxime, but not with cefuroxime, was associated with higher 30 day mortality (adjusted OR 2.24, 95% CI 1.23–4.08 and adjusted OR 1.98, 95% CI 0.98–4.01) than oxacillin or cefazolin.[3] Cefuroxime and ceftriaxone, however, were never directly compared as empirical therapy in SAB. This comparison is highly relevant for clinical practice, since both agents are prescribed in patients with suspected bloodstream infection in order to provide Gram-negative coverage.

Studies investigating pharmacokinetics/pharmacodynamics of ceftriaxone in critically ill patients have suggested that there is substantial risk of failure to maintain adequate antibiotic concentrations against *S. aureus* in all patients with standard ceftriaxone dosing of 2 g once daily.[2,4] Therefore, EUCAST recommends a dosage of 2 g twice daily for *S. aureus* infections.[17] In our study, the majority of patients in the ceftriaxone group received 2 g once daily and no difference in bacteraemia duration was observed in comparison with flucloxacillin. This suggests that patients attain adequate ceftriaxone concentrations for clearance of bacteraemia at the standard dosage. In clinical practice, patients may receive additional dosages due to fixed administration times. Typically, the first dosage of empirical treatment is administered at admission when an infection is suspected, and the second dosage the next morning during standard administration times. Therefore, a patient in whom ceftriaxone is prescribed at standard dosage is likely to receive 2 g twice during the first 24 h of antibiotic administration. Also, empirical antibiotic therapy is typically only administered during a limited time period, until blood culture results become available and directed therapy is initiated. Therefore, even if empirical treatment with ceftriaxone does not lead to optimal antibiotic concentrations, it might not result in worse clinical outcomes since patients only receive empirical antibiotics briefly. Nevertheless, a recent meta-analysis observed similar 90 day mortality in patients receiving ceftriaxone or anti-staphylococcal antibiotics as definite treatment, suggesting that even prolonged treatment with ceftriaxone is safe in SAB.[18] These findings, however, were based on three small, retrospective studies using different antibiotic regimens as comparator, and two studies did not report the ceftriaxone dosage.[19–21] Moreover, the study that included the highest percentage of patients with endocarditis reported increased mortality in the ceftriaxone group, making it difficult to draw definite conclusions regarding the effectiveness of ceftriaxone as definite treatment of MSSA bacteraemia with different foci of infection.[20]

A serious limitation of this study is potential residual confounding by indication. Clinicians base their choice for an empirical agent on patient and disease characteristics, which has probably confounded the effect estimates. This is illustrated by the low frequency of community-acquired infections and severe sepsis and the high prevalence of peripheral venous catheter infections in the flucloxacillin group. We performed a multivariable regression analysis to adjust for confounding by indication. However, since the sample size was limited, there is probably still

residual confounding. Ideally, a randomized study is performed to compare different antibiotic regimens for empirical treatment of MSSA bacteraemia. By definition, such a study must include a more broadly defined group of patients, since only a minority of patients in whom empirical antibiotic therapy is initiated have SAB. Currently, a randomized controlled trial is underway to test whether ceftriaxone is non-inferior to the combination of cefuroxime and an aminoglycoside for empirical treatment of sepsis (Netherlands Trial Register NL9429). However, a previous Dutch study showed an overall blood culture positivity rate of 10.7% and it is estimated that in Dutch hospitals *S. aureus* accounts for 10% of all blood culture isolates.[22,23] Based on these estimates, roughly 100 patients must be randomized after sampling of blood cultures to include one person with microbiologically confirmed SAB. This illustrates how laborious performing an RCT on empirical therapy of SAB is, and it is therefore likely that we keep depending on observational studies like this to inform clinical decision-making. Second, sample size was limited in the flucloxacillin and cefuroxime groups and consequentially the study was insufficiently powered to detect a 2-fold increase in SAB-related mortality. Also, patients received varying dosages of flucloxacillin, raising the question of whether the results can be extrapolated to high-dosage flucloxacillin therapy. Last, blood culture sampling was performed as per routine clinical practice and not at standardized moments, which may have led to detection bias. The number of days between the last positive and first negative blood culture was higher in the cefuroxime group, which could have led to underestimation of bacteraemia duration in this group. Therefore, we performed a sensitivity analysis using an alternative definition of bacteraemia duration, which showed estimates consistent with the primary analysis.

In conclusion, in this study we could not demonstrate a difference in clinical or microbiological outcome between SAB patients empirically treated with flucloxacillin, cefuroxime, or ceftriaxone. Future, preferably randomized studies are needed to investigate whether these results are robust.

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Transparency declarations

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Author contributions

D. T. P. Buis conceived the study protocol together with T. W. van der Vaart, J. M. Prins, J. T. M. van der Meer, M. J. M. Bonten, E. Sieswerda, C. H. van Werkhoven and K. C. E. Sigaloff. T. W. van der Vaart performed data collection. D. T. B. Buis performed all analyses and drafted the manuscript. T. W. van der Vaart, J. M. Prins, J. T. M. van der Meer, M. J. M. Bonten, E. Sieswerda, C. H. van Werkhoven and K. C. E. Sigaloff critically reviewed the manuscript before providing final approval.

Supplementary data

Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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