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Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study

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Objectives: We compared the effectiveness of cefazolin versus cloxacillin in the treatment of MSSA bacteraemia in terms of mortality and relapse.

Methods: A retrospective cohort study examined consecutive patients with *Staphylococcus aureus* bacteraemia from six academic and community hospitals between 2007 and 2010. Patients with MSSA bacteraemia who received cefazolin or cloxacillin as the predominant definitive antibiotic therapy were included in the study. Ninety-day mortality was compared between the two groups matched by propensity scores.

Results: Of 354 patients included in the study, 105 (30%) received cefazolin and 249 (70%) received cloxacillin as the definitive antibiotic therapy. In 90 days, 96 (27%) patients died: 21/105 (20%) in the cefazolin group and 75/249 (30%) in the cloxacillin group. Within 90 days, 10 patients (3%) had a relapse of *S. aureus* infection: 6/105 (6%) in the cefazolin group and 4/249 (2%) in the cloxacillin group. All relapses in the cefazolin group were related to a deep-seated infection. Based on the estimated propensity score, 90 patients in the cefazolin group were matched with 90 patients in the cloxacillin group. In the propensity score-matched groups, cefazolin had an HR of 0.58 (95% CI 0.31–1.08, $P=0.0846$) for 90 day mortality.

Conclusions: There was no significant clinical difference between cefazolin and cloxacillin in the treatment of MSSA bacteraemia with respect to mortality. Cefazolin was associated with non-significantly more relapses compared with cloxacillin, especially in deep-seated *S. aureus* infections.

Keywords: *Staphylococcus aureus*, *S. aureus*, bloodstream infections

Introduction

Staphylococcus aureus bacteraemia (SAB) is a leading bloodstream infection, with 10%–30% mortality.[1–4] Standard treatment for MSSA bacteraemia includes antistaphylococcal penicillins such as cloxacillin.[5,6] Cefazolin, a first-generation cephalosporin available in North America but not in the UK, is also frequently used for MSSA due to its tolerability and convenient dosing. In current guidelines, cefazolin is second-line treatment for MSSA bacteraemia.[5–7]

Type A β-lactamase production in large-inoculum *S. aureus* infection can inactivate cefazolin, which may theoretically contribute to cefazolin treatment failure.[8–11] However, the comparative clinical effectiveness of cefazolin and antistaphylococcal penicillins in SAB is unclear. To our knowledge, only three relatively small cohort studies have compared cefazolin with antistaphylococcal penicillins, and showed no statistical difference in clinical outcomes such as mortality and treatment failure.[12–14] However, statistical insignificance does not translate to no clinical difference. In the three studies, wide CIs that cross 1 do not support the conclusion of no clinical difference.[12–14] In these studies, small sample size and low event rate contributed to the wide CI; sample size was 41–72 in the cefazolin group.[12–14]

We compared the effectiveness of cloxacillin with that of cefazolin as the definitive antibiotic therapy for MSSA bacteraemia in terms of mortality and relapse.

Methods

Study design

We conducted a retrospective cohort study at six acute-care academic and community hospitals in the Greater Toronto Area, which accounted for a total of 2968 acute-care beds and 145000 annual patient admissions. Consecutive patients were recruited from 1 April 2007 to 31 March 2010. Research Ethics Board approval was obtained from each institution. Patient consent for data collection was not obtained due to the retrospective cohort nature of the study. Waiver of consent was approved by all site Research Ethics Boards.

Patients were included if they had at least one positive blood culture for *S. aureus*. Identification of *S. aureus* and antimicrobial susceptibility testing of blood cultures were based on CLSI guidelines.[15]

Patients under the age of 18 were excluded. Additionally, patients were excluded if any of the following occurred within 3 days of blood culture: death; left against medical advice; or deemed palliative. The threshold of 3 days was chosen because >90% of blood cultures returned antibiotic susceptibility results within 3 days. Thus, antibiotic therapy after 3 days was considered to be not empirical, but definitive.

Only patients with MSSA bacteraemia treated with cefazolin or cloxacillin as the predominant antibiotic during their antibiotic course were included in the analysis. The predominant antibiotic was defined as the only antibiotic used for >3 days and for the majority (>50%) of the time during the antibiotic course.

Data collection

Data were obtained from patients' electronic and paper medical records at each site and entered into a standardized case report form. Collected data included patient demographics, comorbidities, microbiological data, antibiotic treatment, investigations and clinical outcomes.

Patient characteristics and SAB clinical characteristics

Nosocomial, healthcare-associated and community-acquired infections were based on standard definitions.[16] Patients were assumed to have community-acquired infection unless proven otherwise.

High- and intermediate-risk cardiac conditions were defined according to American Heart Association guidelines for infective endocarditis.[17] Immune suppression was defined as high-dose corticosteroid (>10 mg of prednisone or equivalent), HIV/AIDS, chemotherapy within the last 6 weeks, neutropenia within 72 h of bacteraemia or transplantation requiring immunosuppressive therapy.

Renal insufficiency was defined as serum creatinine >177 μmol/L within 24 h of bacteraemia. Early infectious foci were defined as documented foci preceding or within 3 days of blood culture collection, whereas late infectious foci were defined as any documented foci after 3 days following blood culture collection. Endocarditis was adjudicated using the modified Duke criteria.[18]

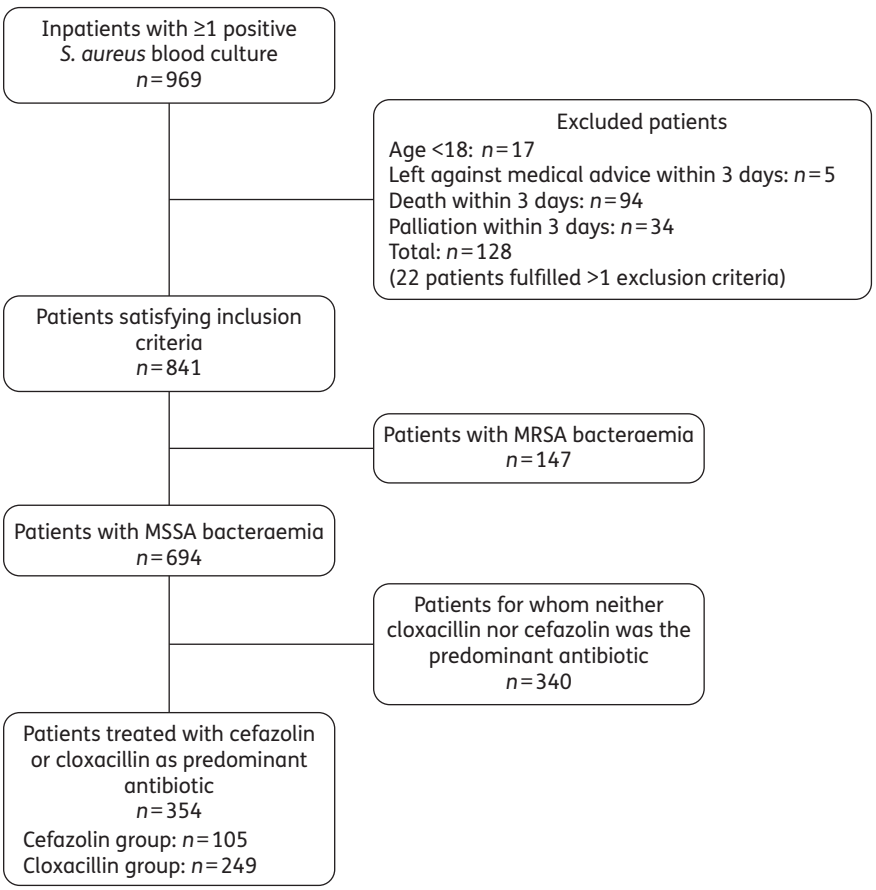

Figure 1. Inclusion of patients in study.

Table 1. Baseline patient and SAB clinical characteristics of cefazolin and cloxacillin groups

	All patients ($n=354$)	Cefazolin ($n=105$)	Cloxacillin ($n=249$)	P value for cefazolin versus cloxacillin
Age (years), median (IQR)	68 (53–79)	69 (55–80)	67 (52–78)	0.2145
Age >65 years	192 (54%)	60 (57%)	132 (53%)	0.4861
Male	224 (63%)	58 (55%)	166 (67%)	0.0532
Hospital site				<0.0001
1	66 (19%)	30 (29%)	36 (14%)	
2	34 (10%)	1 (1%)	33 (13%)	
3	96 (27%)	20 (19%)	76 (31%)	
4	56 (16%)	17 (16%)	39 (16%)	
5	51 (14%)	19 (18%)	32 (13%)	
6	51 (14%)	18 (17%)	33 (13%)	
Admitting service				0.1117
ICU	55 (16%)	10 (10%)	45 (18%)	
medical	219 (62%)	68 (65%)	151 (61%)	
surgical	80 (23%)	27 (26%)	53 (21%)	
Healthcare setting[a]				0.1238
community acquired	118 (33%)	27 (26%)	91 (37%)	
healthcare associated	119 (34%)	41 (39%)	78 (31%)	
nosocomial	117 (33%)	37 (35%)	80 (32%)	
Comorbidity				
high-risk cardiac condition	38 (11%)	10 (10%)	28 (11%)	0.7100
intermediate-risk cardiac condition	14 (4%)	5 (5%)	9 (4%)	0.5662
myocardial infarction	78 (22%)	23 (22%)	55 (22%)	>0.9999
congestive heart failure	80 (23%)	25 (24%)	55 (22%)	0.7811
peripheral vascular disease	36 (10%)	15 (14%)	21 (8%)	0.1224
chronic pulmonary disease	29 (8%)	9 (9%)	20 (8%)	0.8349
connective tissue disease	14 (4%)	5 (5%)	9 (4%)	0.5662
chronic kidney disease	82 (23%)	29 (28%)	53 (21%)	0.2154
haemodialysis	31 (9%)	8 (8%)	23 (9%)	0.6862
diabetes	110 (31%)	33 (31%)	77 (31%)	>0.9999
malignancy	93 (26%)	27 (26%)	66 (27%)	>0.9999
liver cirrhosis	28 (8%)	4 (4%)	24 (10%)	0.0832
immune suppression	65 (18%)	19 (18%)	46 (18%)	>0.9999
At presentation (within 24 h)				
fever	221 (62%)	61 (58%)	160 (64%)	0.2820
hypotensive shock	92 (26%)	32 (30%)	60 (24%)	0.2332
renal insufficiency	78 (22%)	22 (21%)	56 (22%)	0.7809
Infectious foci/complications preceding or within 3 days of blood culture				
intravascular catheter	47 (13%)	13 (12%)	34 (14%)	0.8643
skin and soft tissue	68 (19%)	26 (25%)	42 (17%)	0.1038
respiratory	61 (17%)	17 (16%)	44 (18%)	0.8776
bone and joint	43 (12%)	15 (14%)	28 (11%)	0.4766
abscess	21 (6%)	2 (2%)	19 (8%)	0.0466
endocarditis	32 (9%)	2 (2%)	30 (12%)	0.0018
urinary tract	23 (6%)	6 (6%)	17 (7%)	0.8161
other foci[b]	42 (12%)	7 (7%)	35 (14%)	0.0499
unknown foci	120 (34%)	35 (33%)	85 (34%)	0.9029
embolic stroke	12 (3%)	2 (2%)	10 (4%)	0.5212
ICU admission within 72 h of blood culture	69 (19%)	14 (13%)	55 (22%)	0.0772

Continued

Table 1. *Continued*

	All patients ($n=354$)	Cefazolin ($n=105$)	Cloxacillin ($n=249$)	*P* value for cefazolin versus cloxacillin
Mechanical ventilation within 7 days of blood culture	78 (22%)	16 (15%)	62 (25%)	0.0497
Infectious foci/complications after 3 days of blood culture				
intravascular catheter	5 (1%)	1 (1%)	4 (2%)	>0.9999
skin and soft tissue	13 (4%)	3 (3%)	10 (4%)	0.7623
respiratory	12 (3%)	5 (5%)	7 (3%)	0.3498
bone and joint	28 (8%)	8 (8%)	20 (8%)	>0.9999
abscess	21 (6%)	5 (5%)	16 (6%)	0.6304
endocarditis	10 (3%)	2 (2%)	8 (3%)	0.7294
urinary tract	0 (0%)	0 (0%)	0 (0%)	
other foci[b]	13 (4%)	4 (4%)	9 (4%)	>0.9999
embolic stroke	8 (2%)	1 (1%)	7 (3%)	0.4446

[a]Healthcare setting was defined according to Friedman *et al.*[16] Healthcare-associated infection was defined as a positive blood culture within 2 days of hospital admission from a patient who fulfilled any of the following criteria: (i) attended hospital or haemodialysis clinic or intravenous chemotherapy clinic within 30 days before the infection; (ii) received intravenous therapy at home; (iii) received wound care or nursing care through a healthcare agency; (iv) performed self-administered intravenous medical therapy within 30 days of infection; (v) hospitalized in an acute-care facility within 90 days of infection; or (vi) resided in a long-term care or nursing home. Nosocomial infection was defined as a positive blood culture from a patient admitted to hospital for ≥2 days. Community-acquired infection was defined as a positive blood culture within 2 days of hospital admission from a patient who did not satisfy the criteria for healthcare-associated infection.
[b]Other foci included intra-abdominal infection, biliary tract infection, CNS infection, endovascular infection, mycotic aneurysm, cardiac device infection and any other infectious foci that did not belong in the infectious foci categories.

Antibiotic therapy

For MSSA, appropriate antibiotics included intravenous antistaphylococcal β-lactams, quinupristin/dalfopristin, daptomycin and vancomycin. Duration of antibiotic treatment was calculated from the start of appropriate antibiotic closest to blood culture collection date. For patients discharged alive, the planned treatment stop date was considered as the last day of appropriate antibiotics.

Outcomes

The primary outcome was mortality within 90 days. All patient outcomes were followed until death in hospital or 90 days, whichever came first. Patients were lost to follow-up if they did not return to hospital for follow-up or readmission.

The secondary outcome was relapse, which was defined as any positive culture for *S. aureus* isolated from a suspected infectious focus after discontinuation of an antibiotic course and within 90 days of follow-up. Isolates were considered as relapses unless the susceptibility pattern differed from that of the original SAB.

Statistical analysis

Comparisons between cefazolin and cloxacillin groups were done with the Wilcoxon rank sum test for non-normally distributed continuous variables and Fisher's exact test for categorical variables.

A Cox proportional-hazards regression model was used to characterize 90 day mortality. In the univariate analysis, patient baseline characteristics and SAB clinical characteristics with the exception of variables beyond 3 days were considered potential predictors. All predictors with $P<0.2$ on univariate analysis were included in the final multivariable Cox proportional-hazards regression model along with predominant antibiotic choice.

The propensity score for predominant antibiotic choice was estimated using a logistic regression using all baseline patient characteristics as listed in Table 3. Cefazolin patients were matched in a 1:1 ratio to cloxacillin patients using nearest neighbour matching with a specified calliper width of 0.25 times the standard deviation of the logit of propensity scores.

All reported CIs were two-sided 95% intervals and all tests were two-sided with a $P<0.05$ significance level. All analyses were done with R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 969 patients with at least one positive *S. aureus* blood culture, 354 were eligible for the study, which included 249 (70%) patients who received cloxacillin and 105 (30%) patients who received cefazolin as the predominant antibiotic (Figure 1). Antibiotic therapy and survival for excluded patients are listed in Table S1 (available as Supplementary data at *JAC* Online) and Figure S1. Antibiotic assignment and mortality rate were similar between calendar years (Table S2).

Patient baseline and SAB clinical characteristics

Baseline patient characteristics and SAB clinical characteristics of the cefazolin and cloxacillin groups are listed in Table 1. Among the 354 SAB cases, there was no resistance to cefazolin or cloxacillin based on MIC cut points in the CLSI guidelines.[15]

Antibiotic treatment

Of all patients, 318 (90%) received appropriate antibiotics within 2 days of blood culture: 93/105 (89%) cefazolin patients and 225/249 (90%) cloxacillin patients ($P=0.7004$).

All patients, including those who died while receiving antibiotics, received a median of 18 days (IQR 13–32 days) of

appropriate antibiotics. Cefazolin patients received a median of 17 days (IQR 13–31 days) and cloxacillin patients received a median of 19 days (IQR 13–34 days) of appropriate antibiotics ($P=0.4146$). Cefazolin accounted for a median of 86% (IQR 75%–94%) of total appropriate antibiotic days in cefazolin patients, whereas cloxacillin accounted for a median of 88% (IQR 78%–94%) of total appropriate antibiotic days in cloxacillin patients ($P=0.1957$).

The standard cloxacillin dosage was 8–12 g daily. The median daily dose was 12 g (IQR 8–12 g) for cloxacillin patients. For 19 obese cloxacillin patients (recorded weight >90 kg) the median daily dose was 12 g (range 8–18 g). The standard cefazolin dosage was 3 g daily. The median dose was 3 g (IQR 3–3 g) for cefazolin patients. For seven obese cefazolin patients (recorded weight >90 kg) the median dose was 4 g (range 3–6 g). There were 9/105 (9%) cefazolin patients and 18/249 (7%) cloxacillin patients who received gentamicin as synergistic treatment ($P=0.6648$). No patient received rifampicin.

Management

For early intravascular catheter infection, 7/13 (54%) cefazolin patients and 22/34 (65%) cloxacillin patients had their catheter removed ($P=0.5207$). For early bone or joint infection, 11/15 (73%) cefazolin patients and 13/28 (46%) cloxacillin patients had bone debridement or joint aspiration ($P=0.1161$). For early abscess, 1/2 (50%) cefazolin patients and 12/19 (63%) cloxacillin patients had abscess drainage ($P>0.9999$).

Mortality

Of 354 patients, 96 (27%) died within 90 days: 21/105 (20%) cefazolin patients and 75/249 (30%) cloxacillin patients. Relative to cloxacillin, cefazolin had an HR for 90 day mortality of 0.62 (95% CI 0.38–1.00, $P=0.0497$) (Figure 2).

Significant predictors of 90 day mortality with $P>0.2$ on univariate analysis (Table S3) are listed in Table 2. After adjusting for these variables in a multivariable model, cefazolin had an HR for 90 day mortality of 0.60 (95% CI 0.36–1.01, $P=0.0557$) (Table 2).

Based on propensity scores derived from a multivariable logistic regression, 90 cefazolin patients were matched to 90 cloxacillin patients. After matching, the baseline and SAB clinical characteristics were similar between the two groups (Table 3). The maximum standardized difference of the mean was 0.1240. After matching by propensity score, relative to cloxacillin, cefazolin had an HR for 90 day mortality of 0.58 (95% CI 0.31–1.08, $P=0.0846$) (Figure S2).

Relapse

Of all 354 patients, 10 (3%) had a relapse of *S. aureus* infection: 6/105 (6%) cefazolin patients and 4/249 (2%) cloxacillin patients. In all relapse cases treated with cefazolin, the infectious focus of the original SAB infection or relapse was a deep-seated infection (Table S4). In the groups matched for propensity score, 6/90 (7%) cefazolin patients and 2/90 (2%) cloxacillin patients had a relapse.

Discussion

Our study of consecutive patients with MSSA bacteraemia from six academic and community hospitals between 2007 and 2010

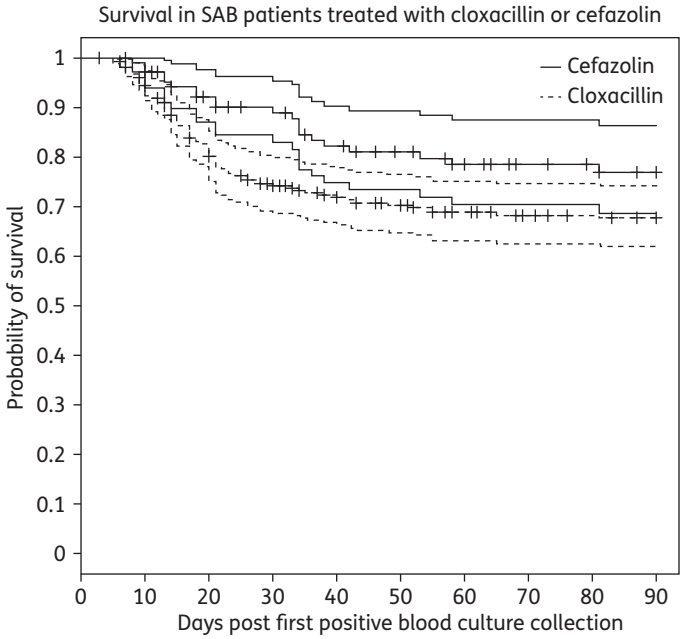

Figure 2. Unadjusted 90 day mortality for cefazolin versus cloxacillin.

Table 2. Final multivariable Cox proportional hazard model predicting 90 day mortality

Variable	HR for 90 day mortality (95% CI)	HR *P* value
Age >65 years	2.53 (1.56–4.11)	0.0002
Male	0.64 (0.41–0.98)	0.0421
Hospital site		
1	0.50 (0.22–1.12)	0.0939
2	reference	
3	0.62 (0.31–1.22)	0.1669
4	0.53 (0.23–1.25)	0.1493
5	0.65 (0.29–1.43)	0.2823
6	0.62 (0.28–1.38)	0.2387
Comorbidity		
congestive heart failure	1.22 (0.74–2.01)	0.4299
chronic kidney disease	1.62 (0.98–2.67)	0.0597
malignancy	1.46 (0.92–2.34)	0.1098
liver cirrhosis	2.06 (1.05–4.05)	0.0350
At presentation (within 24 h)		
fever	0.59 (0.38–0.90)	0.0140
hypotensive shock	1.49 (0.92–2.40)	0.1024
Early SAB infectious foci/complications preceding or within 3 days of blood culture		
intravascular catheter	0.70 (0.31–1.56)	0.3822
skin and soft tissue	0.79 (0.43–1.43)	0.4327
respiratory	1.50 (0.91–2.49)	0.1140
other foci	1.83 (1.00–3.33)	0.0488
embolic stroke	1.80 (0.69–4.65)	0.2279
Cefazolin	0.60 (0.36–1.01)	0.0557

Table 3. Baseline patient characteristics and SAB clinical characteristics between propensity score-matched groups

Variable	Cefazolin ($n=90$)	Cloxacillin ($n=90$)	Standardized difference of mean	Variance ratio
Age >65 years	50 (56%)	52 (58%)	0.0449	0.9880
Male	54 (60%)	50 (56%)	0.0901	1.0288
Hospital site				
1	22 (24%)	20 (22%)	0.0526	0.9358
2	1 (1%)	1 (1%)	0.0000	1.0000
3	20 (22%)	23 (26%)	0.0782	1.1007
4	13 (14%)	14 (16%)	0.0311	1.0629
5	16 (18%)	17 (19%)	0.0287	1.0481
6	18 (20%)	15 (17%)	0.0862	0.8681
Admitting service				
ICU	9 (10%)	11 (12%)	0.0708	1.1920
medical	59 (66%)	58 (64%)	0.0233	1.0148
surgical	22 (24%)	21 (23%)	0.0261	0.9686
Healthcare setting				
community acquired	23 (26%)	24 (27%)	0.0253	1.0279
healthcare associated	33 (37%)	29 (32%)	0.0936	0.9404
nosocomial	34 (38%)	37 (41%)	0.0682	1.0299
Comorbidity				
high-risk cardiac condition	9 (10%)	11 (12%)	0.0708	1.1920
intermediate-risk cardiac condition	4 (4%)	5 (6%)	0.0510	1.2355
myocardial infarction	19 (21%)	19 (21%)	0.0000	1.0000
congestive heart failure	19 (21%)	21 (23%)	0.0535	1.0741
peripheral vascular disease	10 (11%)	12 (13%)	0.0679	1.1700
chronic pulmonary disease	8 (9%)	8 (9%)	0.0000	1.0000
connective tissue disease	5 (6%)	5 (6%)	0.0000	1.0000
chronic kidney disease	21 (23%)	22 (24%)	0.0261	1.0324
haemodialysis	7 (8%)	8 (9%)	0.0402	1.1291
diabetes	28 (31%)	24 (27%)	0.0982	0.9124
malignancy	22 (24%)	21 (23%)	0.0261	0.9686
liver cirrhosis	4 (4%)	2 (2%)	0.1240	0.5116
immune suppression	18 (20%)	16 (18%)	0.0568	0.9136
At presentation (within 24 h)				
fever	54 (60%)	57 (63%)	0.0686	0.9676
hypotensive shock	26 (29%)	24 (27%)	0.0496	0.9519
renal insufficiency	17 (19%)	20 (22%)	0.0826	1.1281
Early SAB infectious foci preceding or within 3 days of blood culture				
intravascular catheter	13 (14%)	12 (13%)	0.0321	0.9351
skin and soft tissue	21 (23%)	20 (22%)	0.0265	0.9662
respiratory	17 (19%)	17 (19%)	0.0000	1.0000
bone and joint	12 (13%)	9 (10%)	0.1040	0.7788
abscess	2 (2%)	4 (4%)	0.1240	1.9545
endocarditis	2 (2%)	2 (2%)	0.0000	1.0000
urinary tract	3 (3%)	5 (6%)	0.1080	1.6284
other foci	7 (8%)	8 (9%)	0.0402	1.1291
unknown foci	29 (32%)	25 (28%)	0.0971	0.9186
embolic stroke	2 (2%)	1 (1%)	0.0869	0.5057
>2 days to appropriate antibiotics	10 (11%)	11 (12%)	0.0346	1.0863

compared patients who received cefazolin with those who received cloxacillin therapy. Our matched propensity score analysis found no significant statistical difference in 90 day mortality. The upper CI of 1.08 suggests that cefazolin is not inferior to cloxacillin and that there is no clinical difference between the two in terms of mortality.

In our multivariate modelling of mortality, significant predictors of mortality included age, gender, liver cirrhosis and fever. These predictors were also described as significant predictors in previous studies.[19,20]

Based on our study estimates, patients treated with cefazolin were less likely to die within 90 days compared with those treated with cloxacillin, but the CI crossed 1. This is consistent with other studies that compared cefazolin with antistaphylococcal penicillin.[12–14] There are a few potential explanations for our estimate of cefazolin predicting a lower risk of death than the aforementioned studies. First, the overall mortality rate in our study differed greatly from rates in other studies. The mortality rates reported in the three studies were 49% at 90 days,[12] 1% at 90 days[14] and 7.3% at 12 weeks.[13] In contrast, our mortality rate, 27%, seemed to approximate more closely the mortality rate in the management of SAB reported in large US, British and Canadian studies.[1,2,4] Second, our large sample size group led to a more precise estimate of mortality.

Although not statistically significant, there were more relapse cases in the cefazolin group compared with the cloxacillin group, which was shown in a past study.[14]

Our study has several strengths. To our knowledge, it is the largest study comparing cefazolin with antistaphylococcal penicillins. The large sample size and number of events for mortality increased the precision of our estimates. Also, our study included multiple academic and community hospitals, enhancing its generalizability. Moreover, our study estimated mortality and relapses separately, unlike the composite outcomes used in past studies.[13,14] Lastly, comparison of cloxacillin versus cefazolin in terms of mortality was analysed using a multivariable model and propensity score-matched analysis. The similar estimates from the two methods make our analyses robust.

Our study has limitations that merit mentioning. First, our data came from a retrospective chart review. However, rigorous and systematic data collection followed by regular data verification ensured that the data were of high quality. Second, we anticipated selection bias to be present with respect to assignment of antibiotics. In our study, patients with deep-seated infections, including endocarditis and abscess, were more likely to receive cloxacillin. Physicians may be reluctant to treat severe infections with cefazolin, which may account for higher mortality in cloxacillin patients. To account for this selection bias, we adjusted for baseline patient characteristics, infectious foci and other SAB clinical characteristics in a multivariable model and propensity score-matched analysis. However, our study could not capture all risk factors for fatal outcome, which is impossible in an observational study. Only a randomized controlled trial (RCT) can adequately balance all such prognostic factors. The propensity-matched analysis included only four endocarditis cases, so our results should not be generalized to treatment of *S. aureus* endocarditis. Third, our definition of predominant antibiotic as >50% of total antibiotic days leaves the possibility of potential crossover of antibiotic treatment, especially in early empirical therapy, which may account for the similarity between the two groups. In our study, crossover in early therapy to cefazolin or cloxacillin was relatively infrequent, at 8% and 14% (Table S5). Also, early empirical antibiotic therapy might have the most impact on early death, which we excluded in our study. A similar definition of predominant antibiotic therapy has been used in a past study.[21] Lastly, the follow-up was different for in-hospital patients and discharged patients in our study. We cannot exclude the possibility that patients who were lost to follow-up could have died outside the hospital. However, most patients in Toronto who are readmitted after discharge return to the same hospital.[22] Also, the mortality rate in our study was similar if not higher than in other SAB cohorts in long-term follow-up, suggesting that we did not miss a significant number of deaths.[23–25] Competing risk models analysing only in-hospital death with hospital discharge as a competing event yielded similar results (Table S6).

Adding to previous studies, our study suggests that cefazolin could be considered along with antistaphylococcal penicillins as first-line treatment for MSSA bacteraemia without any endocarditis or deep-seated infection. A large comparative RCT should be done to confirm our study findings. Until then, it appears that there is no clear difference between the two drugs and clinicians can still choose antibiotic therapy for MSSA based on what is best suited to individual patient characteristics.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S6, Figure S1 and Figure S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Chang FY, MacDonald BB, Peacock JE Jr *et al*. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. *Medicine (Baltimore)* 2003; **82**: 322–32.

2 Wyllie DH, Crook DW, Peto TE. Mortality after *Staphylococcus aureus* bacteraemia in two hospitals in Oxfordshire, 1997–2003: cohort study. *BMJ* 2006; **333**: 281.

3 Kaech C, Elzi L, Sendi P *et al*. Course and outcome of *Staphylococcus aureus* bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. *Clin Microbiol Infect* 2006; **12**: 345–52.

4 Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2006. *J Infect Dis* 2008; **198**: 336–43.

5 Mermel LA, Farr BM, Sherertz RJ *et al*. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001; **32**: 1249–72.

6 Mermel LA, Allon M, Bouza E *et al*. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1–45.

7 Baddour LM, Wilson WR, Bayer AS *et al*. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005; **111**: e394–434.

8 Bryant RE, Alford RH. Unsuccessful treatment of staphylococcal endocarditis with cefazolin. *JAMA* 1977; **237**: 569–70.

9 Fernandez-Guerrero ML, de Gorgolas M. Cefazolin therapy for *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2005; **41**: 127.

10 Nannini EC, Singh KV, Murray BE. Relapse of type A β-lactamase-producing *Staphylococcus aureus* native valve endocarditis during cefazolin therapy: revisiting the issue. *Clin Infect Dis* 2003; **37**: 1194–8.

11 Nannini EC, Stryjewski ME, Singh KV *et al*. Inoculum effect with cefazolin among clinical isolates of methicillin-susceptible *Staphylococcus aureus*: frequency and possible cause of cefazolin treatment failure. *Antimicrob Agents Chemother* 2009; **53**: 3437–41.

12 Paul M, Zemer-Wassercug N, Talker O *et al*. Are all β-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia? *Clin Microbiol Infect* 2011; **17**: 1581–6.

13 Lee S, Choe PG, Song KH *et al*. Is cefazolin inferior to nafcillin for treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia? *Antimicrob Agents Chemother* 2011; **55**: 5122–6.

14 Li J, Echevarria KL, Hughes DW *et al*. Comparison of cefazolin versus oxacillin for the treatment of complicated bacteremia caused by methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2014; **58**: 5117–24.

15 Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement M100-S17*. CLSI, Wayne, PA, USA, 2007.

16 Friedman ND, Kaye KS, Stout JE *et al*. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002; **137**: 791–7.

17 Wilson W, Taubert KA, Gewitz M *et al*. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116**: 1736–54.

18 Li JS, Sexton DJ, Mick N *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; **30**: 633–8.

19 van Hal SJ, Jensen SO, Vaska VL *et al*. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev* 2012; **25**: 362–86.

20 McClelland RS, Fowler VG Jr, Sanders LL *et al*. *Staphylococcus aureus* bacteremia among elderly vs younger adult patients: comparison of clinical features and mortality. *Arch Intern Med* 1999; **159**: 1244–7.

21 Patel UC, McKissic EL, Kasper D *et al*. Outcomes of ceftriaxone use compared to standard of therapy in methicillin susceptible staphylococcal aureus (MSSA) bloodstream infections. *Int J Clin Pharm* 2014; **36**: 1282–9.

22 Gruneir A, Dhalla IA, van Walraven C *et al*. Unplanned readmissions after hospital discharge among patients identified as being at high risk for readmission using a validated predictive algorithm. *Open Med* 2011; **5**: e104–11.

23 Honda H, Krauss MJ, Jones JC *et al*. The value of infectious diseases consultation in *Staphylococcus aureus* bacteremia. *Am J Med* 2010; **123**: 631–7.

24 Pastagia M, Kleinman LC, Lacerda de la Cruz EG *et al*. Predicting risk for death from MRSA bacteremia. *Emerg Infect Dis* 2012; **18**: 1072–80.

25 Forsblom E, Ruotsalainen E, Ollgren J *et al*. Telephone consultation cannot replace bedside infectious disease consultation in the management of *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2013; **56**: 527–35.