J Antimicrob Chemother 2013; **68**: 1894–1900
doi:10.1093/jac/dkt108 Advance Access publication 18 April 2013

Journal of Antimicrobial Chemotherapy

Effectiveness of penicillin, dicloxacillin and cefuroxime for penicillin-susceptible *Staphylococcus aureus* bacteraemia: a retrospective, propensity-score-adjusted case–control and cohort analysis

Jette Lindbjerg Nissen[1,2], Robert Skov[1], Jenny Dahl Knudsen[3], Christian Østergaard[3,4], Henrik Carl Schønheyder[5], Niels Frimodt-Møller[3] and Thomas Benfield[2,6]*

[1]Statens Serum Institut, Copenhagen, Denmark; [2]Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark; [3]Department of Clinical Microbiology, Copenhagen University Hospital, Hvidovre, Denmark; [4]Department of Clinical Microbiology, Copenhagen University Hospital, Herlev, Denmark; [5]Department of Clinical Microbiology, Aarhus University Hospital, Aalborg, Denmark; [6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

*Corresponding author. Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark. Tel: +45-38622302; Fax: +45-38623405; E-mail: tlb@dadlnet.dk

Received 26 December 2012; returned 19 January 2013; revised 23 February 2013; accepted 2 March 2013

Objectives: Penicillin-susceptible *Staphylococcus aureus* isolates account for a fifth of cases of *S. aureus* bacteraemia (SAB) in Denmark, but little is known about treatment outcomes with penicillins or other antimicrobials. Here we compare penicillin, dicloxacillin and cefuroxime as definitive treatments in relation to 30 day mortality.

Methods: A retrospective chart review of 588 penicillin-susceptible *S. aureus* cases at five centres from January 1995 to December 2010. Data on demographics, antimicrobial treatment, clinical signs and symptoms, and mortality at day 30 were collected. Hazard ratios (HRs) with 95% CIs associated with mortality were modelled using propensity-score-adjusted Cox proportional hazards regression analysis. Propensity-score-matched case–control studies were carried out.

Results: Definitive therapy with cefuroxime was associated with an increased risk of 30 day mortality compared with penicillin (adjusted HR 2.54, 95% CI 1.49–4.32). Other variables that were statistically significantly associated with 30 day mortality included increasing age, disease severity and a primary respiratory focus. Osteomyelitis/arthritis was associated with a lower risk of death than were other secondary manifestations. Propensity-score-matched case–control studies confirmed an increased risk of 30 day mortality: cefuroxime treatment (39%) versus penicillin treatment (20%), $P=0.037$; and cefuroxime treatment (38%) versus dicloxacillin treatment (10%), $P=0.004$.

Conclusions: Definitive therapy for penicillin-susceptible SAB with cefuroxime was associated with a significantly higher mortality than was seen with therapy with penicillin or dicloxacillin.

Keywords: sepsis, survival analysis, epidemiology

Introduction

A fifth of invasive cases of *Staphylococcus aureus* bacteraemia (SAB) in Denmark remain susceptible to penicillin and the drug of choice for treatment of penicillin-susceptible *S. aureus* is penicillin.[1] This recommendation is based on *in vitro* data that indicate a superior potency of penicillin over penicillinase-resistant β-lactams.[2] However, observational studies or randomized trials to support the recommendation have not been performed.

Several recent studies have questioned the effectiveness of the antimicrobials frequently used in the treatment of methicillin-susceptible SAB. Paul *et al.*[3] showed a comparable efficacy of cefazolin and cloxacillin, whereas other β-lactams, including second- and third-generation cephalosporins, were associated with a higher mortality. Similarly, Schweizer *et al.*[4] reported significantly lower mortality hazards associated with cefazolin and nafcillin than with vancomycin.

Evidence from randomized clinical trials comparing different antimicrobials for the treatment of infectious diseases is scarce. While randomized trials are central to the collection of efficacy data, these are unlikely to be conducted for off-patent

drugs. In non-randomized studies, the investigator has no control over the treatment assignment, and direct comparisons of the treatment groups may be misleading owing to bias. In the setting of observational data and case series, propensity-score adjustment and matching is a method of reducing the bias between treatment groups.[5,6] The propensity score for an individual is the probability of receiving a given treatment based on the individual's covariate values. Using the score to match and adjust balances the unequal chance of allocation to a treatment group.

We hypothesized that the treatment of penicillin-susceptible SAB with penicillin would lead to improved survival compared with treatment with other antimicrobials.

Methods

Study setting

We conducted a retrospective case series review of consecutive adult (≥16 years) patients with penicillin-susceptible SAB in six hospitals served by three departments of clinical microbiology (DCMs). Cases from Hvidovre, Bispebjerg and Amager Hospitals (DCM Hvidovre) and Herlev and Glostrup Hospitals (DCM Herlev) were included from 1 January 1995 through 31 December 2010. Cases from Aalborg Hospital (DCM Aalborg) were included from 1 January 2004 through 31 December 2009.

The study was approved by the Danish National Board of Health (record number: 7-604-04-2/223/KWH) and the Danish Data Protection Agency (record number: 2001-14-0021). Informed consent is not required by Danish legislation for register-based studies.

Susceptibility testing

Antimicrobial susceptibility testing was carried out initially at the DCMs using disc diffusion and the clover-leaf test. All blood culture isolates of *S. aureus* were routinely referred to the national reference laboratory (Statens Serum Institut, Copenhagen) and retested using disc diffusion, according to the EUCAST guideline, i.e. an inoculum with a turbidity equivalent to that of a 0.5 McFarland standard on Mueller–Hinton agar using a 1 U penicillin disc. After 18–22 h of incubation at 35°C, the zone sizes were read with callipers and the zone edge was inspected. Susceptibility was defined as a zone size ≥26 mm and a fuzzy zone edge.[2]

Data variables

Data extracted from medical charts included age, sex, the origin of the bacteraemia, (community, hospital, healthcare associated or unknown),[7,8] the site of infection associated with the SAB (the primary focus), possible secondary manifestations, injection drug use (IDU), plasma creatinine level (the highest recorded value within 24 h of blood culture), antimicrobial therapy (duration, dose and route of administration) and vital status at day 30.

The Pitt bacteraemia score is a severity of illness grading system evaluating mental status, the presence or absence of fever, hypotension, mechanical ventilation and cardiac status for each patient within the time period of 2 days before and 1 day after the first positive blood culture.[9,10]

Data on co-morbidity were collected from the National Patient Registry (NPR)[11] and used to calculate the Charlson Co-morbidity Index (CCI).[12] We calculated the CCI score by gathering diagnoses from the NPR from up to 10 years prior to the date of SAB and excluding other diagnoses from the admission with SAB. Diagnosis codes in the NPR were coded by physicians at hospital discharge according to the International Classification of Diseases, 8th revision (ICD-8), until the end of 1993 and according to the ICD-10 thereafter.

Time to death (in days) was calculated from the day the first positive blood culture was obtained.

Definitions

Case definitions

Patients above 15 years of age with confirmed penicillin-susceptible SAB were eligible for inclusion.

Empirical antimicrobial treatment

Empirical treatment was defined as any antimicrobial agent administered between the time the blood culture was obtained and the time of the final blood culture result (i.e. identification of *S. aureus* and its susceptibility pattern). Appropriate empirical antimicrobial therapy had to meet the following criteria: the administration of at least one antimicrobial to which the isolate was susceptible *in vitro*, and initiation of therapy within 2 days of blood culture.

Definitive antimicrobial treatment

Definitive treatment was defined as antimicrobial therapy administered after the results of the susceptibility testing had become available and initiated no later than 5 days after blood culture. Definitive treatment was categorized as penicillin, dicloxacillin, cefuroxime or other. Cases treated with penicillin, dicloxacillin and cefuroxime received only that antimicrobial.

Optimal doses were defined as daily dosing with at least 1.2 g of benzylpenicillin every 8 h, 1 g of dicloxacillin every 6 h or 0.75 g of cefuroxime every 8 h.[2]

Combination antimicrobial therapy

Cases receiving more than one antimicrobial agent as the initial treatment were categorized as being treated with combination antimicrobial therapy. The additional antimicrobial drugs were fusidic acid, an aminoglycoside, ciprofloxacin, rifampicin, a macrolide or other.

Statistics

All values are presented as medians and IQRs. Categorical variables were compared using χ^2 statistics. Annual data were divided into three periods (1995–2000, 2001–05 and 2006–10) to assess changes with time.

Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was checked either visually for categorical variables or by Schoenfeld residuals for numerical variables. A test for interaction was performed and interaction terms fitted

accordingly by multiplying the two factors. In univariate analysis, all variables were tested for their association with 30 day mortality. Variables with associations at $P<0.10$ were included in the multivariate analysis. We compared survival times using the log-rank test and presented these as Kaplan–Meier curves. ORs with 95% CIs were computed by conditional logistic regression analysis.

We employed propensity score methods, in which the predicted probability of treatment with cefuroxime was derived from unconditional logistic regression, utilizing a manual backward-elimination approach. The predicted probability of the model was used as the propensity score for each patient. For the propensity-score-matched case–control study, patients in the cefuroxime treatment group were matched with patients in the penicillin treatment group who had the closest propensity scores within a calliper size of one-quarter of the standard deviation of the propensity score. Thus, we excluded cases in which the propensity score difference was more than 0.038. Thirty day mortality was compared between the propensity-score-matched groups. The goodness of fit of the model was tested with the Hosmer–Lemeshow test,[13] which revealed an adequate model fit ($P=0.72$). Data were analysed using IBM SPSS Statistics (version 20; IBM, Armonk, New York, USA).

Results

A total of 795 consecutive patients with penicillin-susceptible SAB were identified. Of these, 207 cases were excluded because of age <16 years ($n=16$), undeterminable definitive antimicrobial therapy ($n=74$), lack of antimicrobial therapy ($n=18$), an ambiguous susceptibility pattern ($n=15$), unavailability of a blood culture isolate for confirmatory penicillin susceptibility testing ($n=28$), death within the first 3 days after the blood culture had been obtained, i.e. prior to reaching the point at which definitive antimicrobial therapy could be received, as per the definition above ($n=52$), and oral antimicrobial therapy ($n=4$). Thus, a total of 588 cases were included in the final analysis.

Antimicrobial treatment

As shown in Table 1, penicillin was the most frequently used single agent for definitive antimicrobial therapy, followed by dicloxacillin and cefuroxime. Thirty-nine per cent of patients received either another agent or combination therapy. Ninety-two per cent started empirical treatment within 1 day of blood culture. A total of 77% and 93% of patients had initiated definitive treatment within 3 and 4 days of blood culture, respectively. Penicillin was used more often in cases with a high Pitt bacteraemia score, community-acquired SAB from Aalborg Hospital, cases with active IDU or cases with a secondary manifestation of endocarditis or meningitis. Cases from Herlev, with a primary focus associated with an intravascular device or dialysis, were more often treated with dicloxacillin. Cases with a primary focus of respiratory infection or an unknown focus were more often treated with cefuroxime.

Among the patients treated with penicillin, 159 of 166 (96%) were optimally dosed. The unadjusted mortality in the penicillin group receiving optimal dosing was 21%, compared with 0% for the seven patients who received suboptimal treatment. In the dicloxacillin group, 61 of 111 (55%) patients were treated with an optimal dose, 42 (38%) with a suboptimal dose and 8 (7%) with an unknown dose. The unadjusted mortality in these groups was 11%, 7% and 25%, respectively. In patients treated with cefuroxime, 80 of 85 (94%) received an optimal dose, three (3.5%) a suboptimal dose and two (2.5%) an unknown dose. The unadjusted mortality was 40%, 33% and 50%, respectively.

Survival

Of the 588 individuals, 121 died within 30 days (20.6%). Survival curve analysis indicated an increased mortality rate associated with cefuroxime at day 30 compared with the other antimicrobials (Figure 1; log-rank test $P=0.001$).

By univariate regression analysis, definitive antimicrobial treatment with cefuroxime compared with penicillin was associated with an increased risk of death at 30 days. Older age, a higher Pitt score and a primary focus of respiratory infection, other foci or an unknown focus were also associated with an increased risk of death. Definitive antimicrobial therapy with dicloxacillin, active IDU, hospital-acquired SAB and osteomyelitis/arthritis were associated with a decreased risk of death (Table 2). Initial treatment, initial combination therapy, inappropriate initial treatment or CCI was not associated with a change in mortality.

The propensity score was derived from an unconditional logistic regression model controlling for age, sex, origin, CCI, primary focus, secondary manifestation, Pitt score, IDU, plasma creatinine, hospital and year. There were interactions between time period and IDU, secondary manifestation and hospital; between hospital and IDU and primary focus; and between origin and age, Pitt score, IDU, primary focus, secondary manifestation and hospital. Terms for each interaction were included in the regression model. Use of cefuroxime for definitive treatment was more likely for women, patients with an unknown origin and a date of 2001 onwards compared with 1995–2000, and was less likely at Amager, Herlev, Glostrup and Aalborg Hospitals compared with Hvidovre Hospital (Table S1, available as Supplementary data at *JAC* Online).

In multivariate analysis, all the variables associated with outcome at $P<0.1$ in the univariate analysis were included and further adjusted for the propensity score. There were interactions between origin and age, Pitt score, IDU and secondary manifestations; between IDU and Pitt score; and between definitive antimicrobial and time. Terms for each interaction were included in the multivariate model. Cefuroxime as the definitive antimicrobial therapy remained significantly associated with a risk of death compared with treatment with penicillin (HR 2.68, 95% CI 1.50–4.78).

A high Pitt score, a primary focus in the lung and 'focus other or unknown' remained independently associated with an increased risk of death. Without propensity-score adjustment, the HR of the association of cefuroxime and mortality was reduced to 2.00 (95% CI 1.16–3.15) (Table 3).

Regression models with dicloxacillin-treated patients as the reference yielded similar estimates of survival. Without and with propensity-score adjustment, the HRs of 30 day mortality were 4.71 (95% CI 2.44–9.09) and 3.44 (95% CI 1.67–7.11), respectively, for cefuroxime-treated compared with dicloxacillin-treated patients. There was no difference in risk of death

Table 1. Characteristics of the study population stratified by definitive treatment group

	Number of patients (%)				
	all ($n=588$)	penicillin ($n=165$)	dicloxacillin ($n=109$)	cefuroxime ($n=85$)	other ($n=229$)
Age group (years)					
≥16–50	129 (22)	32 (25)	30 (23)	10 (8)	57 (44)
51–65	153 (26)	40 (26)	30 (20)	21 (14)	62 (40)
66–80	174 (30)	51 (30)	30 (17)	28 (16)	65 (37)
>80	132 (22)	42 (32)	19 (14)	26 (20)	45 (34)
Female	240 (41)	72 (30)	39 (16)	47 (20)	82 (34)
CCI score					
0	161 (36)	57 (35)	27 (17)	20 (13)	57 (35)
1–2	76 (17)	22 (29)	12 (16)	14 (18)	28 (37)
>2	212 (47)	61 (29)	41 (19)	32 (15)	78 (37)
Pitt bacteraemia score					
0–3	510 (87)	143 (28)	101 (20)	67 (13)	199 (39)
>3	77 (13)	21 (27)	8 (10)	18 (23)	30 (39)
IDU					
no	551 (94)	148 (27)	103 (19)	82 (15)	218 (39)
yes	29 (5)	15 (52)	5 (17)	2 (7)	7 (24)
previous	8 (1)	2 (25)	1 (13)	1 (13)	4 (50)
Origin					
community	234 (40)	71 (30)	33 (14)	38 (16)	92 (40)
hospital	237 (40)	61 (26)	52 (21)	39 (17)	85 (36)
healthcare associated	113 (19)	31 (28)	24 (21)	6 (5)	52 (46)
unknown	4 (1)	2 (50)	0 (0)	2 (50)	0
Primary focus					
intravenous device	57 (10)	11 (19)	16 (28)	7 (12)	23 (41)
dialysis	63 (11)	10 (16)	21 (33)	1 (2)	31 (49)
skin infection	80 (14)	21 (26)	14 (18)	6 (8)	39 (48)
respiratory infection	39 (7)	8 (21)	2 (5)	13 (33)	16 (41)
urinary tract infection	52 (9)	15 (29)	13 (25)	7 (14)	17 (32)
post-operative infection	32 (5)	10 (31)	5 (16)	3 (9)	14 (44)
other	70 (11)	29 (41)	7 (10)	10 (14)	24 (34)
unknown	195 (33)	61 (31)	31 (16)	38 (20)	65 (33)
Secondary manifestations					
none	464 (79)	119 (26)	101 (22)	80 (17)	164 (35)
endocarditis/meningitis	48 (8)	22 (46)	4 (8)	1 (2)	21 (44)
osteomyelitis/arthritis	67 (11)	22 (33)	4 (6)	4 (6)	37 (55)
other	9 (2)	2 (22)	0 (0)	0 (0)	7 (78)
Microbiology service					
Hvidovre	215 (37)	63 (30)	31 (14)	54 (25)	67 (31)
Herlev	277 (47)	58 (21)	69 (25)	25 (9)	125 (45)
Aalborg	96 (16)	44 (46)	9 (9)	6 (6)	37 (39)
Year					
1995–2000	136 (23)	45 (33)	41 (30)	13 (9)	37 (27)
2001–05	198 (34)	57 (29)	25 (13)	37 (19)	79 (40)
2006–10	254 (43)	63 (25)	43 (17)	35 (14)	113 (45)

associated with the use of penicillin or other treatments when compared with dicloxacillin.

Propensity-score-matched case–control study

Fifty-six patients in the cefuroxime treatment group were matched with the 56 patients in the penicillin treatment group who had the closest propensity scores (Table S2, available as Supplementary data at *JAC* Online). The 27 cefuroxime-treated patients who were excluded because they could not be matched to a penicillin-treated patient did not differ with respect to age, sex, origin, CCI, primary focus, secondary manifestation, Pitt score, IDU, plasma creatinine level, hospital or year. The clinical characteristics and demographic data of the patients included were comparable in the matched group (Table 4). Twenty-two patients (39%) in the matched cefuroxime group and 11 patients (20%) in the matched penicillin group died within 30 days [OR 2.65 (95% CI 1.13–6.19), $P=0.025$]. Three patients were suboptimally dosed with either penicillin or cefuroxime. Removal of the data for these three patient pairs did not affect the result. Among the recipients of cefuroxime, 22 of 53 (42%) died, compared with 10 of the 53 recipients of penicillin (19%) ($P=0.019$).

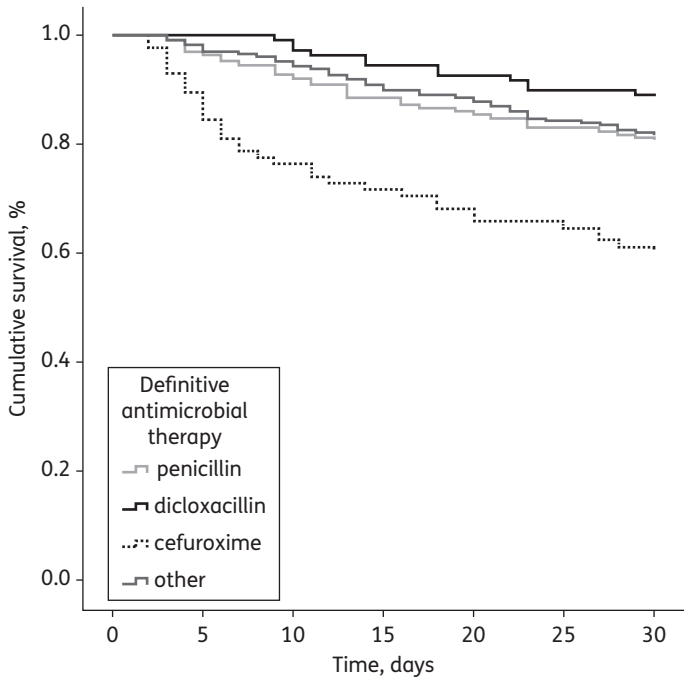

Figure 1. Thirty day survival curves after SAB according to definitive antimicrobial treatment. Log-rank test $P=0.001$.

Similarly, we matched 45 patients in the cefuroxime treatment group with 45 patients in the dicloxacillin treatment group by propensity score (Table S2, available as Supplementary data at *JAC* Online). Seventeen patients (38%) in the cefuroxime group died within 30 days compared with seven in the dicloxacillin group (16%), corresponding to an OR of 3.30 (95% CI 1.21–9.02, $P=0.02$). The two groups did not differ with regard to age, sex, CCI, origin, primary focus, secondary manifestation, IDU or Pitt score. Twenty-three patients were suboptimally dosed with dicloxacillin or cefuroxime. After removing these patients' data, the mortality rates were compared but the difference was no longer statistically significant [two of 22 (9%) dicloxacillin-treated patients died compared with seven of 22 (32%) cefuroxime-treated patients; $P=0.13$].

Subgroup analyses

In subgroup multivariate analysis, cefuroxime as definitive therapy compared with penicillin remained associated with death for patients with (HR 24.14, 95% CI 1.44–464.65) or without (HR 2.01, 95% CI 1.14–3.54) a respiratory focus.

Individuals with low and high Pitt scores had an increased risk of 30 day mortality. With a Pitt score >3, the HR for cefuroxime

Table 2. Propensity-score-adjusted multivariate analysis of 30 day mortality among 588 cases of penicillin-susceptible SAB

	Deaths, *n* (%)	Survivors, *n*	Multivariate HR (95% CI)	*P*
Pitt bacteraemia score, per increment	—	—	1.37 (1.07–1.77)	0.01
Primary focus				
intravenous device	3 (5)	54	1.0	
dialysis	5 (8)	58	1.44 (0.36–5.81)	0.61
skin infection	11 (14)	69	2.01 (0.60–6.72)	0.26
respiratory infection	17 (44)	22	8.05 (2.49–26.02)	0.001
urinary tract infection	8 (15)	44	1.27 (0.37–4.46)	0.70
surgical wound infection	2 (6)	30	0.99 (0.18–5.56)	0.99
other	16 (23)	54	1.86 (0.39–8.98)	0.44
unknown	59 (30)	136	4.16 (1.44–12.06)	0.01
Definitive antimicrobial treatment				
penicillin	33 (19)	132	1.0	
dicloxacillin	12 (11)	97	0.77 (0.38–1.58)	0.49
cefuroxime	34 (40)	51	2.68 (1.50–4.78)	0.001
other	43 (19)	186	1.20 (0.72–2.00)	0.50

Table 3. Risk of 30 day mortality for the cefuroxime-treated group compared with the penicillin-treated group

	HR (95% CI)	*P*
Crude	2.41 (1.49–3.89)	0.0001
Multivariate	2.00 (1.16–3.15)	0.013
Propensity-score adjusted	2.68 (1.50–4.78)	0.001

compared with penicillin was 4.27 (95% CI 1.14–16.05), whereas with a Pitt score of 0–3, the HR was 2.81 (95% CI 1.50–5.28).

Discussion

This propensity-score-adjusted and -matched case–control study showed that treating penicillin-susceptible SAB with cefuroxime led to poorer short-term outcomes compared with treatment with either penicillin or dicloxacillin. To our knowledge, such an association has never been reported before for penicillin-susceptible SAB.

A major potential bias of our study is confounding by indication, i.e. that physicians may tend to use cefuroxime for more serious infections due to a perception of its broader coverage despite microbiological identification of the causative microorganism and its antimicrobial susceptibility profile. Using propensity scores to adjust for a skewed use of cefuroxime, penicillin and dicloxacillin can reduce this bias by balancing covariates in the different treatment groups. Our analyses showed that the HR of death was largely unchanged when adjusted or not adjusted for the propensity score (2.46 versus 1.92). Our matched case–control study showed an OR for 30 day mortality of 2.71–5.16 when cefuroxime treatment was given compared with penicillin or dicloxacillin. None of the other covariates differed between treatment groups after propensity score matching. Furthermore, we used stratified analyses to reduce bias. An analysis of patients with more severe disease showed that the effect estimate was unchanged by stratification. This was true in two situations that may affect physician prescribing: a high Pitt score and a pulmonary focus. This indicates that our results are robust, and we believe the differences in treatment outcomes suggest that penicillin or an antistaphylococcal penicillin is the drug of choice for the treatment of penicillin-susceptible SAB. Further studies are required to determine whether this is also the case for non-bacteraemic infections caused by penicillin-susceptible *S. aureus*. Our study also warrants a clinical trial to confirm our findings in a controlled setting.

The mechanistic basis for the difference in efficacy of cefuroxime and penicillins is unknown. The inoculum effect, i.e. that specific *S. aureus* strains produce large amounts of β-lactamase(s), has been suggested to be the basis of clinical failure in patients suffering high-burden staphylococcal disease such as endocarditis. Cephalosporins are generally resistant to β-lactamases but may be hydrolysed by specific types. However, *in vitro* data indicate that this is not the case for cefuroxime.[14] Another possible explanation could relate to changes in penicillin-binding proteins (PBPs). One strategy to induce resistance to β-lactam antibiotics includes the alteration of endogenous PBPs by point mutations or homologous recombination.[15] Sequencing of PBP1, PBP2 or PBP3 among *S. aureus* treatment failures may determine whether mutations exist that have a differential effect on penicillin and cefuroxime leading to different affinities of the two β-lactams for PBPs.

Table 4. Clinical characteristics of 112 patients with penicillin-susceptible SAB who were included in the propensity-score-matched analysis

	Number of patients (%), unless otherwise stated		
	penicillin treated, *n*=56	cefuroxime treated, *n*=56	*P* value
30 day mortality	11 (20)	22 (39)	0.037
Age (years), median (IQR)	75 (62–86)	70 (57–81)	0.15
Female	28 (50)	27 (48)	1.00
Pitt score, median (IQR)	1 (0–2)	1 (0–2)	0.59
CCI score			
0	15 (31)	12 (28)	
1–2	10 (20)	9 (21)	
≥3	24 (49)	22 (51)	0.96
Origin			
community	25 (45)	23 (41)	
hospital	23 (41)	26 (46)	
healthcare associated	7 (13)	6 (11)	
unknown	1 (1)	1 (2)	0.95
Primary focus			
intravenous device	3 (5)	6 (11)	
dialysis	0 (0)	1 (2)	
skin infection	6 (11)	5 (9)	
respiratory infection	5 (9)	5 (9)	
urinary tract infection	5 (9)	4 (7)	
surgical wound infection	3 (5)	3 (5)	
other	10 (18)	9 (16)	
unknown	24 (43)	23 (42)	0.94
Secondary manifestations			
none	50 (89)	51 (91)	
endocarditis/meningitis	2 (4)	1 (2)	
osteomyelitis/arthritis	3 (7)	4 (7)	0.95
IDU			
no	53 (95)	54 (96)	
yes	3 (5)	1 (2)	
previous	0 (0)	1 (2)	0.36
Hospital			
Hvidovre	16 (29)	17 (30)	
Amager	7 (13)	5 (9)	
Bispebjerg	12 (21)	8 (14)	
Herlev	8 (14)	11 (20)	
Glostrup	5 (9)	9 (16)	
Aalborg	8 (14)	6 (11)	0.69
Period			
1995–2000	12 (21)	11 (20)	
2001–05	25 (45)	20 (36)	
2006–10	19 (34)	25 (44)	0.49

A third option is differences in the pharmacokinetic and pharmacodynamic activity of the different antimicrobials. The optimal time for plasma drug concentrations to remain above the MIC has been estimated to be 40% for penicillins and 50% for cephalosporins.[16] With estimated mean MICs for penicillin-susceptible *S. aureus* of 0.032 mg/L for benzylpenicillin, 0.125 mg/L for dicloxacillin and 1 mg/L for cefuroxime, and based on pharmacokinetic data for the three antimicrobials,[17] the free non-protein-bound plasma drug concentration time > MIC would be roughly 50% for cefuroxime dosing with 1.5 g every 8 h, but <40% for dosing with 750 mg every 8 h, 67% for dicloxacillin (dosing with 1 g every 6 h) and 100% for benzylpenicillin (dosing with 1.2 g every 8 h). This indicates that cefuroxime carries the greatest risk of falling short of the optimal pharmacokinetic/pharmacodynamic parameter. However, crude survival rates did not differ for individuals dosed below or at these levels, and therefore other unknown mechanisms may be in play.

To our knowledge, our study is the first to address a differential effect of antimicrobial choice on the outcome of bacteraemia with penicillin-susceptible *S. aureus*. Interestingly, in a recent study from Israel, second- and third-generation cephalosporins were associated with a poorer outcome for methicillin-susceptible SAB in comparison with cefazolin.[3]

Our study is limited by a small sample size; in particular, a subset of individuals was included in the case–control studies. Furthermore, treatment groups were assigned retrospectively. Nevertheless, two different methodologies have demonstrated comparable increases in the risk of death associated with treatment with cefuroxime. Clinical inferences from our study should, however, be made with caution until a randomized clinical trial has been performed.

In conclusion, we have shown that the treatment of penicillin-susceptible SAB with cefuroxime compared with penicillin or dicloxacillin was associated with a significantly higher mortality. A clinical trial comparing the two treatments is warranted. Studies are also needed to determine whether this is a class effect for cephalosporins or whether it relates specifically to cefuroxime.

Funding

The project was in part funded by The Danish Council for Independent Research (Health and Disease).

Transparency declarations

None to declare.

Supplementary data

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

References

1 Statens Serum Institut. *Annual Report on Staphylococcus aureus Bacteraemia Cases in Denmark 2009 (Part I)*. http://www.ssi.dk/Forskning/Forskningsomraader/Infektioner/Systemiske%20infektioner/~/media/Indhold/DK%20-%20dansk/Forskning/Infektioner/SAB%202009%20part%20I%20final.ashx (16 March 2013, date last accessed).

2 EUCAST. *Breakpoint tables for interpretation of MICs and zone diameters*. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_2.0_120221.pdf (16 March 2013, date last accessed).

3 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.

4 Schweizer ML, Furuno JP, Harris AD *et al*. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. *BMC Infect Dis* 2011; **11**: 279.

5 Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. *Biometrics* 1996; **52**: 249–64.

6 D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**: 2265–81.

7 Garner JS, Jarvis WR, Emori TG *et al*. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16**: 128–40.

8 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.

9 Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents* 1999; **11**: 7–12.

10 Hill PC, Birch M, Chambers S *et al*. Prospective study of 424 cases of *Staphylococcus aureus* bacteraemia: determination of factors affecting incidence and mortality. *Intern Med J* 2001; **31**: 97–103.

11 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**: 30–3.

12 Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.

13 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 1982; **115**: 92–106.

14 Nannini EC, Stryjewski ME, Singh KV *et al*. Determination of an inoculum effect with various cephalosporins among clinical isolates of methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2010; **54**: 2206–8.

15 Zapun A, Contreras-Martel C, Vernet T. Penicillin-binding proteins and β-lactam resistance. *FEMS Microbiol Rev* 2008; **32**: 361–85.

16 Dagan R, Klugman KP, Craig WA *et al*. Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. *J Antimicrob Chemother* 2001; **47**: 129–40.

17 Chambers HF. Penicillins and β-lactam inhibitors. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 7th edn. Philadelphia, PA: Churchill Livingstone Elsevier, 2010; 309–22.