ORIGINAL ARTICLE INFECTIOUS DISEASES

Are all beta-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia?

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Abstract

Methicillin-sensitive *Staphylococcus aureus* (MSSA) is susceptible to many beta-lactams. We compared cloxacillin and cefazolin, the first-line recommended antibiotics, and other beta-lactams in the treatment of MSSA bacteraemia. This was a retrospective cohort study. Included were adult patients with clinically-significant MSSA bacteraemia treated with a beta-lactam that was started within 48 h after blood cultures were taken. We separated between empirical treatment administered to the patient before receipt of final blood culture results and definitive treatment administered thereafter. Univariate and multivariable analyses for 30-day (empirical treatment) and 90-day (definitive treatment) mortality were conducted, including the type of beta-lactam administered to the patient. Five-hundred and forty-one patients were included for the analysis of empirical treatment and 498 patients alive at 7 days were evaluable for definitive treatment. Empirical treatment with cloxacillin or cefazolin (n = 131) was associated with lower 30-day mortality as compared with cefuroxime (n = 98, p 0.058), ceftriaxone or cefotaxime (n = 194, p 0.008) and beta-lactam-beta-lactamase combinations (n = 61, p 0.013), with adjusted odds ratios (OR) for death ranging from 1.98 to 2.68. Definitive treatment with cefazolin (n = 72) was not significantly different from cloxacillin (n = 281); adjusted OR for 90-day mortality 0.91 (95% confidence interval 0.47–1.77). Treatment with cefazolin both in the empirical and definitive periods was not significantly different from cloxacillin; adjusted OR 0.81 (95% confidence interval 0.18–3.62). Treatment of MSSA bacteraemia with cefazolin is not significantly different from treatment with cloxacillin, while treatment with other beta-lactams, including second and third generation cephalosporins, might be associated with higher mortality.

Keywords: Bacteraemia, beta-lactam, cefazolin, empirical antibiotic treatment, methicillin-sensitive *Staphylococcus aureus*, oxacillin
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Background

Beta-lactamase-producing strains of methicillin-sensitive *Staphylococcus aureus* (MSSA) are preferably treated with a semi-synthetic penicillin (e.g. nafcillin or oxacillin). A first-generation cephalosporin is an alternative [1]. Whether penicillins or cefazolins are more efficacious is unknown. Other beta-lactams provide coverage against MSSA; however, they do not appear in recommendations for treatment and their clinical efficacy against invasive MSSA infections is unclear.

It is a common clinical scenario to face a patient coming from the community with severe sepsis and suspected staphylococcal infection. In locations where community-acquired MRSA is not endemic, the physician would debate whether to use a beta-lactam specific for MSSA, a broader-spectrum beta-lactam (e.g. ceftriaxone), which would cover Gram-negative bacteria as well, or both. After identification of MSSA, the main dilemma is between oxacillin (or another penicillin) and cefazolin, although we do not know whether other beta-lactams provide similar efficacy.

The optimal design for comparing beta-lactams in the treatment of invasive staphylococcal infections is a randomized controlled trial. Such a trial is difficult to conduct and has not been performed to date. We compared outcomes for patients given different beta-lactams for the treatment of MSSA bacteraemia in a retrospective cohort

study, attempting to adjust for the differences between patients treated with narrow vs. broad-spectrum beta-lactams.

Methods

Design

This was a retrospective cohort study. The study was approved by the local ethics committee.

Setting

The study was carried out at the Rabin Medical Center, Beilinson Hospital. Data were collected between 1988–1994 and 1999–2007.

Participants

Patients with growth of MSSA in blood were identified through the microbiology laboratory records. Data were collected for all patients in whom MSSA was identified at least in two separate sets of blood cultures or those who fulfilled criteria for systemic inflammatory response syndrome within 48 h of a positive blood culture with no other source of infection. Repeat episodes were included only with an interval of 1 year or more between episodes. Cases of polymicrobial bacteraemia were excluded, unless appropriate antibiotic treatment for the co-pathogen was instituted empirically.

We included in the current analysis only patients treated with a beta-lactam antibiotic that was started within 48 h after collection of positive blood cultures (e.g. appropriate empirical and definitive antibiotic treatment). Referring to the clinical questions, we classified empirical treatment into five categories: cloxacillin, penicillin if susceptible or cefazolin; cefuroxime; ceftriaxone or cefotaxime; beta-lactam-beta-lactamase combinations; and other beta-lactams (other cephalosporins and carbapenems). Definitive treatment was classified into three categories: cloxacillin/penicillin; cefazolin; and other beta-lactams. A subgroup analysis of definitive treatment was conducted restricted to patients who received the same empirical and definitive treatment.

Treatment given to the patient during the first 2 days after collection of blood cultures was recorded as the empirical treatment and that given on days 3–9 (first week after receipt of blood culture results) was recorded as definitive treatment. We did not consider further treatment, because it might have been influenced by patients' responses to previous treatment (clinical failure, success or persistence of bacteraemia). The analysis of definitive treatment was restricted to patients alive at day 7. All patients are included in the analysis of empirical antibiotic treatment.

Variables

The outcome considered was 30-day all-cause mortality for empirical antibiotic treatment. For definitive treatment, we assessed 90-day mortality, as in previous studies [2,3], considering that the definitive antibiotic regimen was usually continued for 2–4 weeks. To examine risk factors for death and to compare between study groups we collected a large dataset of variables pertaining to patient demography (including place of infection acquisition and functional status), background conditions, risk factors specific for staphylococcal bacteraemia (indwelling catheters and other devices, invasive procedures, etc.), clinical presentation, source of bacteraemia and severity of sepsis, laboratory measurements on the day of blood culture collection and infection management (including removal of foreign devices). All data were obtained through patient chart review and the electronic hospital records. Mortality data were derived from the Israeli Internal Ministry registry. Hospital-acquired infection was defined when blood cultures were taken 48 h or more after admission and healthcare-associated infections were defined as previously suggested [4]. All antibiotic treatment from the date of blood culture collection until 30 days was recorded.

Microbiology

Staphylococci were identified using the Slidex-Staph Kit (bioMerieux, France), the Pastorex Staph (Sanofi Diagnostics, Pasteur) slide agglutination test confirmed by DNase or the API-Staph test (bioMerieux, France). Antibiotic susceptibility was tested using the disk diffusion method on Mueller–Hinton agar, according to contemporaneous NCCLS or CLSI standards. We considered all beta-lactam-beta-lactamase combinations, cephalosporins and carbapenems as covering, regardless of susceptibility testing. Penicillin derivatives (e.g. piperacillin and mezlocillin) were considered covering only if the isolate was susceptible to penicillin or if the antibiotic was tested and found covering.

Statistical analysis

To identify the risk factors for death we compared dichotomous variables using a chi-square test and continuous variables using a *t*-test or the Mann–Whitney *U*-test, as appropriate. To exclude variables with high co-linearity from the multivariate analysis, variables significantly associated with 30-day mortality on univariate analysis were assessed for bivariate correlation using Spearman's ρ test. We excluded from further analysis significantly correlated variables ($p < 0.001$ and R between 0.26 and 0.71), selecting the more clinically relevant variable in correlated pairs. Selected variables were entered as covariates into a conditional forward

stepwise logistic regression analysis for 30-day mortality for empirical and definitive treatment. The type of beta-lactam was forced into each model. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. The fit of the model was tested using the Hosmer-Lemeshow goodness of fit test and its prediction using the area under the ROC curve (AUC) generated by predicted probabilities. Analyses were conducted using PASW statistics 17.0 (SPSS, Inc).

Results

Out of 771 clinically significant episodes of MSSA bacteraemia, 541 episodes could be evaluated for empirical treatment and 498 patients alive on day 7 were evaluated for definitive treatment (Fig. 1). Patient characteristics are detailed in Table 1. Infections were rarely acquired in the community without contact with the healthcare setting. More than 50% of patients died within 1 year following the bacteraemia.

There were significant differences in baseline patient characteristics between patients treated empirically with targeted therapy against MSSA (oxacillin or cefazolin) and those given broader-spectrum beta-lactams (data not shown). Mortality at 30 days without adjustment for these differences was 22.1% (29/131) for empirical treatment with cloxacillin or cefazolin compared with 34.7% (34/98) with cefuroxime, 50.5% (98/194) with ceftriaxone/cefotaxime, 41% (25/61) with beta-lactam-beta-lactamase combinations and 28.1% (16/57) with other beta-lactams ($p < 0.001$ overall). Empirical treatment with vancomycin was not associated with 30-day mortality [32/82 (39%) with vancomycin vs. 170/459 (37%) without vancomycin combination therapy, p 0.732]. In the adjusted analysis for empirical antibiotic treatment, beta-lactams other than cloxacillin or cefazolin were associated with higher 30-day mortality (Table 2). The adjusted OR for empirical treatment with cefuroxime was 1.98 (95% CI 0.98–4.01), for ceftriaxone or cefotaxime 2.24 (95% CI 1.23–4.08) and for beta-lactam-beta-lactamase combinations 2.68 (95% CI 1.23–5.85). For other beta-lactams (mainly ceftazidime) mortality was not significantly different from cloxacillin/cefazolin, but most patients were treated in combination with vancomycin and confidence intervals were wide. Other risk factors for 30-day mortality are shown in Table 2. The model's calibration and predictive performance were adequate.

Considering definitive antibiotic treatment, there were no statistically significant differences in 90-day mortality with different beta-lactams in the unadjusted analysis: 32.4% (91/281) with cloxacillin, 40.3% (29/72) with cefazolin and 42.1% (61/145) with other beta-lactams. There was no significant difference in 90-day mortality between definitive treatment with cefazolin vs. cloxacillin in the adjusted analysis; OR 0.91 for all 498 patients evaluated and OR 0.81 for the subgroup of 204 patients treated with cefazolin or cloxacillin both empirically and definitively (Table 3). Mortality was higher with other beta-lactams (OR 1.29, 95% CI 0.77–2.14 overall, and OR 1.64, 95% CI 0.79–3.38 for the subgroup analysis), but

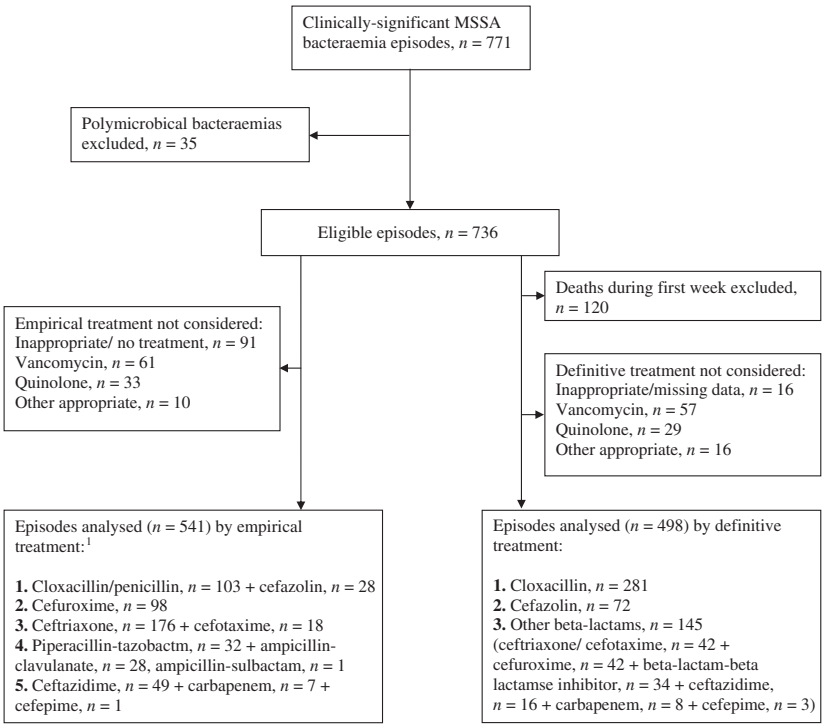

FIG. 1. Patient selection. [1]Vancomycin was administered empirically together with the beta-lactam in 9/131 (6.9%) patients in group 1; 0% in group 2; 23/194 (11.9%) in group 3; 16/61 (26.2%) in group 4 and 34/57 (59.6%) patients in group 5.

TABLE 1. Patient characteristics

Variable	*n*/541 (%) unless otherwise noted
Age (years), mean (SD)	69 (16.8)
Female sex	243 (44.9)
Admitted from home	392/505 (72.5)
Functional capacity	
Independent	295 (54.5)
Assistance in daily activities	114 (21.1)
Bedridden	132 (24.4)
Place of infection acquisition[a]	
Community	66 (12.2)
Healthcare associated	207 (38.3)
Hospital	268 (49.5)
Previous antibiotic treatment within 30 days	230 (42.5)
Hospitalization department	
Medical	421 (77.8)
Surgical	92 (17)
ICU	28 (5.2)
Diabetes	168 (31.1)
Malignancy	152 (28.1)
Chronic renal failure	122 (22.6)
Haemodialysis	21 (3.9)
Congestive heart failure	86 (15.9)
Valvular heart disease[b]	62 (11.5)
Surgery 30 days before infection	108 (20)
Shock at onset of infection	66 (12.2)
Number of positive blood culture bottles >4	82/415 (19.8)
Polymicrobial bacteraemia	41 (7.6)
Source of infection	
Skin/soft tissue	83 (15.3)
Surgical wound infection	49 (9.1)
Bone or joint	27 (5)
Endocarditis	25 (6.5)
Catheter-related	63 (11.6)
Other endovascular	41 (7.6)
Pneumonia	54 (10)
Other documented source[c]	25 (4.6)
Primary/unknown	122 (22.6)
Persistence of bacteraemia >5 days	46 (8.5)
Relapse of bacteraemia within 1 year	12 (2.2)
Mortality at 48 h	52 (9.6)
Mortality at 30 days	202 (37.3)
Mortality at 90 days	266 (49.2)
Mortality at 1 year	315 (58.2)

[a]Bacteraemia was considered hospital acquired when blood cultures were taken more than 48 h after admission. Healthcare acquisition was defined for: patients receiving intravenous therapy, chemotherapy, haemodialysis, wound care or specialized nursing care, or those who attended a hospital clinic within 30 days before bacteraemia; patients hospitalized in an acute care hospital ≥2 days within 90 days; or those residing in a nursing home or long-term care facility.
[b]Including prosthetic valve in 32 patients.
[c]Other sources of infection included abdominal, central nervous system and abscesses.

TABLE 2. Multivariable logistic regression analysis for 30-day mortality: empirical antibiotic treatment[a]

Variable[b]	OR, 95% CI *n* = 541 patients, deaths = 202	p-value
Empirical antibiotic treatment		
Oxacillin/cefazolin	Reference	
Cefuroxime	1.98 (0.98–4.01)	0.058
Ceftriaxone/cefotaxime	2.24 (1.23–4.08)	0.008
Beta-lactam-beta-lactamase	2.68 (1.23–5.85)	0.013
Other beta-lactams	0.81 (0.35–1.9)	0.629
Age (per 1 year increment)	1.04 (1.02–1.06)	<0.001
Female sex	1.69 (1.08–2.63)	0.021
Poor functional capacity (bedridden)	1.73 (1.02–2.93)	0.041
Malignancy	1.89 (1.15–3.09)	0.012
Shock at onset	5.61 (2.75–11.45)	<0.001
Urea (per 1 mg/dL increment)	1.01 (1.007–1.016)	<0.001
Albumin (per 1 mg/dL increment)	0.54 (0.38–0.78)	0.001
Thrombocytes (per 1 K/μL increment)	0.996 (0.994–0.998)	<0.001
Mechanical ventilation	Not retained in final model	0.078
Skin/soft tissue source of infection		0.111

[a]Significance of the model's constant p 0.004, Hosmer and Lemeshow, p 0.71, area under ROC curve for model's prediction of 30-day mortality 0.84 (95% CI 0.81–0.88), p <0.001.
[b]The following variables were significantly associated with mortality on univariate analysis, but not used in the multivariable analysis due to significant correlation with other included variables: MSSA isolation in specimens other than blood cultures, urinary catheter, recent surgery, use of corticosteroids before onset of infection, chronic renal failure, congestive heart failure, dementia and primary source of infection. CI, confidence interval; OR, odds ratio.

the differences were not statistically significant. Fewer variables could be assessed in the model for patients treated with the same beta-lactam empirically and definitively (Table 3), although both models retained adequate predictive performance, with similar results.

Discussion

We compared different beta-lactams in the treatment of MSSA bacteraemia. Addressing different clinical scenarios we separated the empirical treatment phase (first 48 h, before receipt of final blood culture results and susceptibilities) and definitive antibiotic treatment (administered thereafter). Empirical treatment with beta-lactams other than cloxacillin or cefazolin was associated with higher 30-day mortality compared with treatment with these recommended antibiotics. Specifically, third generation cephalosporins (ceftriaxone and cefotaxime) and beta-lactam-beta-lactamase combinations were associated with more than double the odds for death, adjusted to other risk factors for mortality. The main comparison of definitive antibiotic treatment was between cloxacillin and cefazolin. There was no significant difference between them in 90-day mortality; adjusted OR 0.91, 95% CI 0.47–1.77. The data for other beta-lactams in the definitive phase were too sparse for assessment of their effects on mortality.

Previous studies have established the superiority of beta-lactam treatment over glycopeptides for MSSA [2,3,5–8]. In most of these studies any beta-lactam was considered as adequate treatment for MSSA and compared with vancomycin. Two studies specifically assessed cloxacillin [8] and cefazolin [3]. Advantage of the beta-lactam was reported by all studies but it is difficult to compare their results because of the different outcomes reported (bacteraemia persistence, relapse, infection-related mortality, etc.). Direct comparisons between different beta-lactams are scarce. *In-vitro*, it has been reported that penicillinase-resistant penicillins were more resistant to the inoculum effect and to staphylococcal beta-lactamase than first-generation cephalosporins, suggesting better efficacy of the former [9]. Wynn *et al.* compared different antibiotics given as outpatient parenteral antimicrobial therapy (OPAT) for various MSSA infections, including the beta-lactams ceftriaxone, cefazolin, oxacillin and nafcillin. In

TABLE 3. Multivariable logistic regression analysis for 90-day mortality: definitive antibiotic treatment

Variable	All definitive *n* = 498, deaths = 181[a]		Subgroup definitive *n* = 204, deaths = 71[b]	
Variable[c]	OR (95% CI)	p-value	OR (95% CI)	p-value
Definitive antibiotic treatment				
Oxacillin	Reference		Reference	
Cefazolin	0.91 (0.47–1.77)	0.781	0.81 (0.18–3.62)	0.782
Other beta-lactam	1.29 (0.77–2.14)	0.332	1.64 (0.79–3.38)	0.184
Age (per 1-year increment)	1.05 (1.03–1.07)	<0.001	1.04 (1.01–1.06)	0.004
Poor functional capacity (bedridden)	2.33 (1.31–4.13)	0.004	Not included	
Hospital-acquired bacteraemia	2.3 (1.44–3.67)	0.001	2.26 (1.14–4.47)	0.019
Diabetes	1.8 (1.12–2.9)	0.015	Not included	
Malignancy	2.54 (1.51–4.27)	<0.001	2.52 (1.18–5.36)	0.017
Valvular heart disease	2.38 (1.22–4.64)	0.011	Not included	
Urea (per 1 mg/dL increment)	1.008 (1.003–1.013)	0.001	1.01 (1.002–1.018)	0.018
Albumin (per 1 mg/dL increment)	0.4 (0.27–0.58)	<0.001	0.48 (0.27–0.83)	0.008
Thrombocytes (per 1 K/μL increment)	0.997 (0.995–0.999)	0.003	Not included	
Shock at onset of infection	Not retained in final model	0.066	Not included	
Mechanical ventilation		0.054	Not included	
Primary source of infection		0.058	Not included	

[a]Significance of the model's constant p 0.01, Hosmer and Lemeshow p 0.685, area under ROC curve for model's prediction of 90-day mortality 0.84 (95% CI 0.80–0.87), p <0.001.
[b]Subgroup of patients who received the same empirical and definitive antibiotic treatment. Significance of the model's constant p 0.059, Hosmer and Lemeshow p 0.616, area under ROC curve for model's prediction of 90-day mortality 0.78 (95% CI 0.72–0.85), p <0.001.
[c]The following variables were significantly associated with mortality on univariate analysis, but not used in the multivariable analysis due to significant correlation with other included variables: urinary catheter, chemotherapy, chronic renal failure, congestive heart failure, dementia and presence of a foreign body. CI, confidence interval; OR, odds ratio.

the OPAT setting cephalosporins might offer an advantage due to a more convenient administration schedule. No differences were observed in the outcome 'Did the clinical outcome meet expectations?' and with regard to adverse events necessitating treatment discontinuation. Only a few patients with bacteraemia were assessed in each of the beta-lactam categories (11–17 patients) [10]. A small study described similar mortality for MSSA meningitis treated with cefuroxime compared with penicillins [11]. We are not aware of a randomized controlled trial comparing different beta-lactams in the treatment of MSSA infections.

The main limitation of the present analysis is that treatment selected by clinicians was confounded by underlying patient characteristics. Probably no method can fully adjust for the differences between patients given cloxacillin or cefazolin empirically and those treated with broader spectrum beta-lactams. We attempted to adjust for these differences using multivariable regression analysis. While the model constructed was highly predictive, we cannot be sure that all differences between patients treated with narrow vs. broad-spectrum beta-lactams were adjusted for. Once MSSA is identified, a comparison between cloxacillin and cefazolin is more valid, because there is no information regarding whether one or the other treatment is superior. However, this analysis was limited by the paucity of patients treated with cefazolin, resulting in wide confidence intervals. We limited the analysis of definitive antibiotic treatment to the first week because treatment modifications after this period were frequently dictated by patients' responses to the initial treatment regimen. For similar reasons we did not consider the overall treatment duration and antibiotic combinations with aminoglycosides and rifampin. Combination treatment is rare in our centre because there is no evidence for its effect on survival [12,13] and combination treatment did not significantly affect survival in this cohort (data not shown). A distinctive feature of our cohort was that truly community-acquired bacteraemias were rare (12.2%). We used contemporaneous definitions for healthcare-associated bacteraemia and our electronic healthcare system allows for a very high precision in identifying patients' exposure to the healthcare system before hospitalization.

In summary, we present the first analysis attempting to compare different beta-lactams in the treatment of MSSA bacteraemia. Empirical treatment with oxacillin or cefazolin was associated with lower 30-day mortality than other beta-lactams. Definitive treatment with cefazolin or cloxacillin resulted in similar 90-day mortality rates. These results are severely hampered by the association between the treatment regimen selected by clinicians and underlying patient characteristics. This study highlights the difficulties in comparing treatments in a non-randomized design. Many questions regarding the treatment of invasive *S. aureus* infections in general and MSSA bacteraemia in particular exist, including the type of antibiotic, combination therapy and duration of treatment. These questions should be answered in randomized controlled trials.

Transparency Declaration

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