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Davis, J. S.; Turnidge, J.; Tong, S. Y.C.

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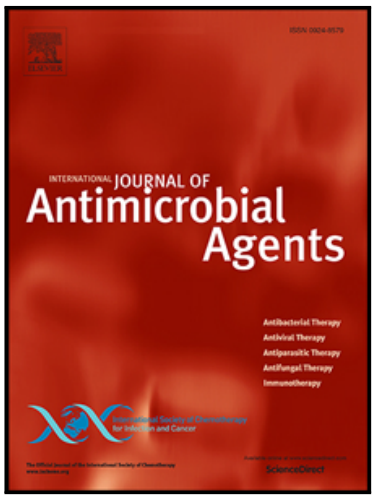

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A large retrospective cohort study of cefazolin compared with flucloxacillin for methicillin-susceptible Staphylococcus aureus bacteraemia

Davis JS[1,2], Turnidge J[3], Tong SYC[1,4]

1. Global and Tropical Health Division, Menzies School of Health Research, Darwin, NT, Australia
2. Department of Infectious Diseases, John Hunter Hospital, Newcastle, NSW Australia
3. Adelaide Medical School, University of Adelaide, South Australia
4. Victorian Infectious Disease Service, The Royal Melbourne Hospital, and The University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia

Corresponding Author

A/Prof Joshua Davis

Joshua.Davis@menzies.edu.au

C/- Menzies School of Health Research, Rocklands Drive, Tiwi, NT 0810, Australia

Telephone +61-488 191938

Short running title

Cefazolin compared with flucloxacillin for methicillin-susceptible Staphylococcus aureus bacteraemia

Keywords

Cefazolin; Flucloxacillin; Anti-staphylococcal penicillins; Staphylococcus aureus; Bacteraemia

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ABSTRACT

Background and objectives

Antistaphylococcal penicillins (ASPs) are recommended as first line treatment for invasive infections caused by methicillin-susceptible Staphylococcus aureus (MSSA). Cefazolin is an alternative option, but there is theoretical concern about using it due to the fact that some MSSA strains produce beta-lactamases active against cefazolin. We aimed to compare outcomes from patients with MSSA infections treated with flucloxacillin and cefazolin.

Methods

We analysed data from The Australia and New Zealand Co-operative Outcomes of Staphylococcal Sepsis (ANZCOSS) observational study, which included all consecutive unique episodes of *Staphylococcus aureus* bacteraemia from 27 hospital-based or independent microbiology laboratories from January 2007 to September 2013. In this retrospective analysis of prospectively collected data, we compared 30-day all-cause mortality in patients with MSSA bacteraemia treated with flucloxacillin to those treated with cefazolin.

Results

We included data from 7,312 episodes of MSSA bacteremia and found no difference in 30-day mortality in those treated with flucloxacillin (731/6520 [11.2%, 95% CI 10.9-12.5%]) compared to cefazolin (83/792 [10.7%, 95% CI 8.4 to 12.8%]), OR 0.93 (95% CI 0.72 to 1.17). In a propensity-adjusted analysis, mortality remained non-significantly lower in the cefazolin group (aOR 0.86 [95% CI 0.65-1.14]).

Conclusions

This study supports the results from previous observational studies from other regions, while extending them to Australasia and to a much larger number of patients. While this observational study suggests cefazolin is likely to have equivalent or superior outcomes to ASPs for MSSA bacteraemia, this can only be convincingly proven by a properly designed randomised controlled trial.

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Introduction

The standard recommended treatment for invasive methicillin-susceptible *Staphylococcus aureus* (MSSA) infections is an anti-staphylococcal penicillin (ASP), such as nafcillin, oxacillin or flucloxacillin. Cefazolin, a first generation cephalosporin, is an alternative option, but guidelines recommend it as second line therapy (e.g., in the case of a minor penicillin allergy) due to theoretical concerns about its efficacy (1). MSSA strains produce a variety of beta-lactamases, to which ASPs are stable. Some MSSA strains demonstrate an *in-vitro* "inoculum effect" to cefazolin, whereby a high inoculum (10^7cfu/ml) is associated with a several-fold increase in MIC compared to a standard inoculum (10^5 cfu/ml)(2). This is usually due to the production of a type A beta-lactamase which is active *in-vitro* against cefazolin. This led to concerns about treatment failure with cefazolin in selected MSSA strains, and early case reports of the same (3, 4). However, cefazolin has some potential advantages over ASPs, including a longer half-life and a lower tendency to cause phlebitis. In recent years, several observational studies have been published that suggest that outcomes for patients with invasive MSSA infections treated with cefazolin are equivalent to or possibly even superior to those treated with ASPs (5-10), and that both the safety profile and cost of cefazolin are superior (11, 12). However, with one exception (8) these studies have been small (range 93 to 354 patients) and are subject to regional variation due to differing prevalence of MSSA strains that produce type A beta-lactamases (3, 13).

Here we report an analysis of a large prospectively collected dataset of consecutive *Staphylococcus aureus* bacteremia episodes from Australia and New Zealand. Our hypothesis was that 30-day mortality is not significantly different in patients treated for MSSA bacteremia with cefazolin as definitive therapy compared to those treated with flucloxacillin.

Patients and Methods

The Australia and New Zealand Co-operative Outcomes of Staphylococcal Sepsis (ANZCOSS) study collected data on all consecutive unique *Staphylococcus aureus* bacteremia episodes from 27

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hospital-based or independent microbiology laboratories in Australia and New Zealand, from January 2007 to September 2013 (14). Prospective approval was provided by the human research ethics committee or local research governance office of each participating hospital or laboratory. Recurrent *Staphylococcus aureus* bacteremia in the same individual was counted as a separate episode if the blood culture was drawn more than 14 days after the previous episode. Data were collected by each laboratory on patient demographics, comorbidities, treatment and outcome and submitted to a central web-based database. Completeness of data was checked at regular intervals by the central data management team and queries sent to each participating laboratory. The requirement for individual participant consent was waived by the approving human research ethics committees.

Site investigators were asked to indicate the "definitive antibiotic agent" used to treat the *Staphylococcus aureus* bacteremia episode in question, defined as the intravenous agent used once the susceptibility profile of the isolate was known.

For the present analysis, a subset of the full ANZCOSS dataset was used, which included only those patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia, and only those whose definitive treatment was either flucloxacillin or cefazolin.

Categorical variables were compared using Chi-squared tests, and continuous using Mann Whitney U tests for non-normal and Student's t tests for normal data. Bivariate logistic regression models were built with 30-day mortality as the outcome variable, and each candidate covariate as the independent variable. Those covariates which differed between the cefazolin and flucloxacillin groups ($p<0.10$) were included in a multivariable logistic regression model to adjust for confounding. In addition, a propensity score was calculated using a logistic regression model with treatment used (flucloxacillin or cefazolin) as the outcome measure. Treatment propensity-adjusted analysis was then performed using inverse probability of treatment weighting. All analyses were carried out

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using Stata version 12 (Statacorp, College Station, Texas). P-values of ≤0.05 were considered significant.

Results

The full ANZCOSS dataset contained data on 13,107 episodes of *Staphylococcus aureus* bacteremia. From this dataset, 2,907 episodes were methicillin-resistant and were excluded. Of the 10,200 MSSAs, 2,352 had definitive treatment other than cefazolin or flucloxacillin (690 vancomycin, 425 not treated, 341 benzylpenicillin, 158 piperacillin/tazobactam, 147 ticarcillin/clavulanate, and 591 other). Of the remaining 7,848, vital status at day 30 was missing for 536, and these were excluded. Hence the final dataset contained 7,312 episodes of MSSA bacteraemia.

Those treated with cefazolin were less likely to be children, or to be male and more likely to be receiving haemodialysis or to have a device-related infection **(table 1).** The unadjusted 30-day mortality did not differ between the flucloxacillin group (731/6520, 11.2%, 95% CI 10.9-12.5%) and the cefazolin group (83/792, 10.7%, 95% CI 8.4 to 12.8%, p=0.53).

In a logistic regression model, the odds ratio for 30 day mortality in the cefazolin group compared with the flucloxacillin group was 0.93 (95% CI 0.72 to 1.17). In a multivariate model adjusting for all covariates which significantly differed between the two treatment groups (gender, age, haemodialysis, device-related infection, and endocarditis), the point estimate for 30-day mortality risk was further lowered in the cefazolin group (OR 0.84, 95% CI 0.63 to 1.11), but this remained not statistically significant. The propensity-matched analysis gave a very similar result, with the adjusted odds ratio for 30 day mortality of 0.86 in the cefazolin group (95% CI 0.65-1.14).

In the subgroup with endocarditis (n=571) which is theoretically a high-inoculum infection, there was also no significant difference in 30-day mortality (5/47 [10.6%] died in the cefazolin group compared with 82/442 [15.6%] in the flucloxacillin group). In a logistic regression model including only endocarditis patients, the raw odds ratio for mortality was 0.64 (95% CI 0.25-1.67) in the cefazolin

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group, and when adjusted for age, gender, device-related infection and haemodialysis, the aOR was 0.49 (95% CI 0.16-1.47).

Discussion

In this large observational study, we found no significant difference in the 30-day mortality in more than 7,000 patients with MSSA bacteraemia whose definitive antibiotic treatment was cefazolin compared to those treated with flucloxacillin. This adds to the growing weight of evidence suggesting that outcomes in MSSA bacteraemia patients treated with cefazolin are not worse than those treated with an ASP.

In the only other study to include a large sample size (n=3,167), McDanel and colleagues found a larger and statistically significant mortality benefit in those treated with cefazolin compared to nafcillin or oxacillin (adjusted OR 0.63, 95% CI 0.51-0.78)(8). Multiple smaller studies have also found a lower odds ratio for 30-day mortality in MSSA bacteraemia patients treated with cefazolin compared with ASPs, with a similar effect size to our study, but these differences were generally not statistically significant (5-7, 9, 10).

Despite several case reports, theoretical concerns about MSSA strains that produce type A beta-lactamase and/or those that exhibit the inoculum effect do not seem to have translated into any consistent clinical signal in large observational studies. However, it is important to note that observational studies are highly prone to selection bias, since patients whom clinicians choose to treat with cefazolin are likely to be systematically different to those whom clinicians choose to treat with ASPs. Multivariate models and adjustment for propensity scores cannot completely eliminate such selection bias, as unmeasured confounders are likely to be present.

The key strength of our study is that it is the largest published to date examining this question, and is broadly representative of Australian and New Zealand patients and MSSA isolates over a 7 year period. By virtue of the study design, to facilitate the inclusion of a large number of patients from

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multiple centres, only relatively sparse data were collected. We did not collect data on source control, detailed comorbidities or safety outcomes; nor were isolates examined for beta-lactamase type or the inoculum effect. However, we believe the data that were collected are accurate, as regular audits for data discrepancies and potential duplicate entries were conducted and resolved with each of the participating sites on a regular basis during data collection. Furthermore, since only definitive therapy was collected, we are unable to assess the contribution of empiric regimens to outcomes. It is possible (albeit unlikely) that empiric regimens were different in the flucloxacillin cefazolin groups and future studies should include such data.

The weight of published evidence should now provide sufficient equipoise for a randomised controlled trial (RCT) to be conducted, comparing cefazolin with one or more ASPs for the definitive treatment of MSSA bacteraemia. Such a trial could reasonably include higher risk patients such as those with endocarditis, and should also collect *in-vitro* data about the cefazolin inoculum effect and type A beta-lactamase production for pre-planned subgroup analysis. It should include safety outcomes, including nephrotoxicity, hepatotoxicity and phlebitis as endpoints, as well as cost effectiveness analyses.

In summary, the present study supports the results from previous observational studies from Asia, USA and Europe, while extending them to Australasia and to a much larger number of patients. While this observational study suggests cefazolin is likely to have equivalent or superior outcomes to ASPs such as flucloxacillin for MSSA bacteraemia, this can only be convincingly proven by a properly designed randomised controlled trial.

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Declarations

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Competing Interests: None

Ethical Approval: Prospective approval was provided by the human research ethics committee or local research governance office of each participating hospital or laboratory.

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Table 1 – Characteristics and outcomes according to definitive antibiotic treatment

	Flucloxacillin (n=6,520)	Cephazolin (n=792)	P-value
Demographics and risk factors			
Gender male	4260 (65.3%)	461 (58.2%)	<0.001
Infant (age<=12 months)	251 (3.9%)	10 (1.3%)	<0.001
Child (age<=16 years)	694 (10.6%)	35 (4.4%)	<0.001
Mean age (adults, n=6,582)	60.8 (19.3)	60.9 (17.7)	NS
Nosocomial acquisition*	558 (33.7%)	56 (32.3%)	NS
On haemodialysis	519 (8.9%)	149 (20.8%)	<0.001
Focus of infection			
Device-related infection	2,056 (33.2%)	281 (37.1%)	0.03
Primary blood stream infection	809 (12.4%)	99 (12.5%)	NS
Endocarditis	524 (8.0%)	47 (5.9%)	0.04
Skin and soft tissue infection	1,185 (18.2%)	148 (18.7%)	NS
Osteoarticular infection	1,195 (18.3%)	128 (16.2%)	NS
Deep abscess	163 (2.5%)	22 (2.8%)	NS
CNS infection	162 (2.5%)	12 (1.5%)	NS
Outcomes			
Admitted to intensive care unit.	878 (13.5%)	110 (13.9%)	NS
Length of hospital stay (days, median [IQR])	20 (11-37)	18 (9-34)	0.002
7-day mortality	294 (4.5%)	29 (3.7%)	NS
30-day mortality	731 (11.2%)	83 (10.5%)	NS

*Denominator=1,655 for flucloxacillin and 174 for cefazolin as data on acquisition status was missing for the remainder

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