Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with Staphylococcus aureus bacteraemia


Published in:
Clinical Microbiology and Infection

DOI:
10.1016/j.cmi.2019.03.010

Published: 01/07/2019

Document Version
Publisher's PDF, also known as Version of record

Link to publication

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 14. Mar. 2020
Systematic review

Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with Staphylococcus aureus bacteraemia

S. Weis 1, 2, 3, *, M. Kesselmeier 2, 4, J.S. Davis 5, 6, A.M. Morris 7, S. Lee 8, A. Scherag 2, 4, 9, S. Hagel 1, 2, †, M.W. Pletz 1, †

1) Institute for Infectious Diseases and Infection Control, Jena University Hospital, Jena, Germany
2) Center for Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany
3) Department of Anesthesiology and Intensive Care, Jena University Hospital, Jena, Germany
4) Research Group Clinical Epidemiology, CSCC, Jena University Hospital, Jena, Germany
5) Department of Infectious Diseases, John Hunter Hospital, Newcastle, NSW, Australia
6) Global and Tropical Health Division, Menzies School of Health Research, Darwin, NT, Australia
7) Department of Medical Microbiology, Research Group Clinical Epidemiology, CSCC, Jena University Hospital, Jena, Germany
8) Department of Internal Medicine, Pusan National University School of Medicine and Medical Research Institute, Pusan National University Hospital, Busan, Republic of Korea
9) Department of Infectious Diseases, John Hunter, Newcastle, NSW, Australia

Keywords:
Anti-staphylococcal penicillins
Antimicrobial therapy
Bacteraemia
Cefazolin
Flucloxacillin
Meta-analysis
Staphylococcus aureus

A B S T R A C T

Background: For patients with bacteraemia caused by methicillin-sensitive Staphylococcus aureus anti-staphylococcal penicillins (ASPs) or cefazolin are agents of choice. While ASPs are potentially nephrotoxic, cefazolin may be less effective in some S. aureus strains due to an inoculum effect.

Objectives: To perform a systematic literature review and meta-analysis assessing current evidence comparing cefazolin with ASPs for patients with S. aureus bacteraemia (SAB).

Methods: We searched MEDLINE, ISI Web of Science (Science Citation Index Expanded) and the Cochrane Database as well as clinicaltrials.gov from inception to 26 June 2018. All studies investigating the effects of cefazolin versus ASP in patients with methicillin-sensitive SAB were eligible for inclusion regardless of study design, publication status or language. Additional information was requested by direct author contact. A meta-analysis to estimate relative risks (RRs) with the corresponding 95% confidence intervals (CIs) was performed. Statistical heterogeneity was estimated using I². The primary endpoint was 90-day all-cause mortality. The Newcastle–Ottawa Scale (NOS) and Grading of Recommendations Assessment, Development and Evaluation (GRADE) were used for study and data quality assessment.

Results: Fourteen non-randomized studies were included. Seven reported the primary endpoint (RR 0.71 (0.50, 1.02), low quality of evidence). Cefazolin treatment may be associated with lower 30-day mortality rates (RR 0.70 (0.54, 0.91), low quality of evidence) and less nephrotoxicity (RR 0.36 (0.21, 0.59), low quality of evidence)). We are uncertain whether cefazolin and ASP differ regarding treatment failure/relapse as the quality of the evidence has been assessed as very low (RR of 0.84 (0.59, 1.18)). For patients with endocarditis (RR 0.71 (0.12, 4.05), RR 0.36 (0.12, 4.05)), cefazolin treatment may be associated with equal 30-day and 90-day mortality (low quality of evidence).

Conclusions: Cefazolin seemed to be at least equally as effective as ASPs while being associated with less nephrotoxicity. S. Weis, Clin Microbiol Infect 2019;25:818

© 2019 The Authors. Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Staphylococcus aureus bacteraemia (SAB) is an often underestimated and common disease [1,2] with reported annual incidence rates of 10–32 cases/100 000 inhabitants [3]. If treated
insufficiently, mortality rates can reach up to 50% and recurrences are frequent [1,4]. Outcomes of SAB can be improved with routine infectious disease consultations that enhance adherence to treatment guidelines, including choice of appropriate antibiotic agent [5]. Treatment of patients with methicillin-sensitive S. aureus (MSSA) bacteraemia relies on the intravenous administration of antibiotics with high anti-staphylococcal activity. Anti-staphylococcal penicillins (ASP) such as flucloxacillin, nafcillin or cloxacillin are considered first-line agents for the treatment of bacteraemia caused by MSSA strains [6].

Whether the first-generation cephalosporin cefazolin is as effective as ASPs is an ongoing matter of debate [7–9]. Based on in vitro studies, it is considered vulnerable to the so-called ‘inoculum effect’ describing an increase in the minimum inhibitory concentration (MIC) in the presence of a large number of bacteria as expected particularly in endocarditis, osteomyelitis, septic arthritis, pneumonia and large abscesses [10,11]. This inoculum effect is mostly observed with specific strains of MSSA, which produce a type A beta-lactamase. The prevalence of MSSA strains exhibiting a cefazolin inoculum effect varies depending on the geographic region and ranges from 19 to 27% in the USA [12,13], from 26 to 46% in South America [14], from 13 to 58% in South Korea [12,15] and is only 6% in Japan [16]. The clinical implications of this in vitro phenomenon on the treatment of MSSA infections, however, are unclear [13]. In addition, due to its broader bacterial spectrum, there is concern that complications such as Clostridium difficile enteritis or the selection of multi-resistant bacteria may be more likely to occur with cefazolin than with ASPs [17]. Conversely, cefazolin has a longer half-life and thus is more convenient to dose compared to nafcillin or oxacillin and appears to be less nephro- and hepatotoxic than ASPs [6].

We aimed to perform a systematic literature review and meta-analysis to assess current available clinical evidence comparing cefazolin with anti-staphylococcal penicillins for patients with SAB. Furthermore, we were interested in whether the outcome of patients with a potentially higher pathogen load, i.e. patients with endocarditis or abscesses, had a worse outcome when treated with cefazolin as compared with ASPs.

Materials and methods

Eligibility criteria

All studies investigating the effects of cefazolin versus ASP in patients with methicillin-sensitive SAB were eligible for inclusion regardless of study design, publication status or language. There was no minimal number of patients. The primary endpoint was 90-day all-cause mortality. Secondary endpoints included 30-day all-cause mortality, treatment failure/relapse and nephrotoxicity. Given the varying description for relapse and that some studies associated with high pathogen load. Two additional subgroups were performed. The first comprised studies comparing cefazolin to nafcillin treatment as this ASP was used in the majority of studies. The second was restricted to studies applying propensity score matching, i.e. matched patients according to their propensity score. This did not include studies with propensity score adjustment in their analyses. In case, subgroups or respective outcome parameters were not reported in the primary publication, authors of the included studies were asked to provide additional information.
### Table 1
Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>No. of centres</th>
<th>Study period</th>
<th>Treatment comparison: cefazolin vs.</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai et al., 2015</td>
<td>Retrospective, non-randomized, propensity score matched cohort study</td>
<td>Canada</td>
<td>6</td>
<td>04/2007–03/2010</td>
<td>Cefazolin</td>
<td>90-d mortality</td>
<td>Relapse</td>
<td>354</td>
</tr>
<tr>
<td>Davis et al., 2018</td>
<td>Retrospective, non-randomized, cohort study</td>
<td>Australia, New Zealand</td>
<td>27</td>
<td>10/2007–09/2013</td>
<td>Flucloxacillin</td>
<td>30-d mortality, LOS</td>
<td>Admission to intensive care unit, 7-d mortality, LOS</td>
<td>7312</td>
</tr>
<tr>
<td>Flint et al., 2017</td>
<td>Retrospective, non-randomized, cohort study</td>
<td>USA</td>
<td>4</td>
<td>11/2013–10/2015</td>
<td>Nafcillin</td>
<td>Acute kidney injury</td>
<td>30-d mortality, 60-d recurrence, microbiological failure, LOS, costs</td>
<td>149</td>
</tr>
<tr>
<td>Kimmig et al., 2018</td>
<td>Retrospective, non-randomized cohort study</td>
<td>Germany</td>
<td>1</td>
<td>12/2012–08/2015</td>
<td>Flucloxacillin</td>
<td>In-hospital mortality</td>
<td>Relapse, hospital readmission, complications, acute renal failure with vancomycin therapy, organ failure</td>
<td>192 in the subgroup of patients treated with cefazolin and flucloxacillin, 297 in total</td>
</tr>
<tr>
<td>Lee et al., 2011</td>
<td>Retrospective, non-randomized, propensity score matched cohort study</td>
<td>Korea</td>
<td>1</td>
<td>01/2004-06/2009</td>
<td>Nafcillin</td>
<td>Treatment failure 4 and 12 weeks</td>
<td>Survival 4 weeks and 12 weeks, interruption to adverse drug events, mean time to defervescence</td>
<td>82</td>
</tr>
<tr>
<td>Lee et al., 2018</td>
<td>Prospective, non-randomized observational cohort study</td>
<td>Korea</td>
<td>10</td>
<td>09/2013–03/2015</td>
<td>Nafcillin</td>
<td>Treatment failure</td>
<td>Mortality</td>
<td>242</td>
</tr>
<tr>
<td>Li et al., 2014</td>
<td>Retrospective, non-randomized cohort study</td>
<td>USA</td>
<td>2</td>
<td>01/2008–06/2012</td>
<td>Oxacillin</td>
<td>Clinical cure at the end of treatment</td>
<td>Treatment failure, 30-, 90-d mortality, adverse events, acute kidney injury</td>
<td>93</td>
</tr>
<tr>
<td>McDanel et al., 2017</td>
<td>Retrospective, non-randomized cohort study</td>
<td>USA</td>
<td>119</td>
<td>2003–2010</td>
<td>Nafcillin/Oxacillin</td>
<td>30-d mortality, 90-d mortality</td>
<td>Recurrence up to 1 year</td>
<td>3167</td>
</tr>
<tr>
<td>Monogue et al., 2018</td>
<td>Retrospective, non-randomized cohort study</td>
<td>USA</td>
<td>1</td>
<td>11/2011–08/2014</td>
<td>Nafcillin</td>
<td>Treatment failure</td>
<td>Adverse drug events</td>
<td>142</td>
</tr>
<tr>
<td>Paul et al., 2011</td>
<td>Retrospective, non-randomized cohort study</td>
<td>Israel</td>
<td>1</td>
<td>1988–1994, 1999–2007</td>
<td>Cloxacillin</td>
<td>30-d mortality for empiric treatment; 90-d mortality for definitive treatment</td>
<td>—</td>
<td>30-d mortality with empirical treatment with cloxacillin/ penicillin 103, with cefazolin 28; 90-d mortality with definitive treatment with cloxacillin 281, with cefazolin 72</td>
</tr>
<tr>
<td>Pollet et al., 2016</td>
<td>Retrospective, non-randomized cohort study</td>
<td>USA</td>
<td>1</td>
<td>01/2008–07/2013</td>
<td>Nafcillin</td>
<td>90-d mortality</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>Rao et al., 2015</td>
<td>Retrospective, non-randomized cohort study</td>
<td>USA</td>
<td>2</td>
<td>01/2010–04/2013</td>
<td>Oxacillin</td>
<td>Treatment failure</td>
<td>All cause in hospital mortality, adverse events (including kidney injury), duration of bacteraemia Length of hospital stay, hospitalization costs, adverse drug reactions Rates of drug-emergent events</td>
<td>27</td>
</tr>
<tr>
<td>Renaud et al., 2011</td>
<td>Retrospective, non-randomized cohort study</td>
<td>Singapore</td>
<td>1</td>
<td>06/2009–12/2009</td>
<td>Cloxacillin</td>
<td>30-d mortality and recrudescence</td>
<td>—</td>
<td>485</td>
</tr>
<tr>
<td>Youngster et al., 2014</td>
<td>Retrospective, non-randomized cohort study</td>
<td>USA</td>
<td>1</td>
<td>2007–2011</td>
<td>Nafcillin</td>
<td>Premature antimicrobial discontinuation</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* d, day; LOS, length of stay.*
Results

Our database search revealed 385 reports. One study was in press but did not appear on the literature search [27] (Table 1, Fig. 1). A total of 69 duplicates were removed. From the remaining 317 references, 303 studies were excluded due to lack of relevant information regarding our predefined outcome parameters. Finally, we identified and analysed 14 studies that had investigated at least one of the outcome parameters. All studies were cohort studies. None of the studies was randomized. All but one study relied on a retrospective data collection [9]. The majority of the studies were conducted in the USA (n = 8) and were single centre (n = 8). Among the included studies, the ASP of choice was nafcillin in six studies, cloxacillin in three studies, oxacillin in three studies, flucloxacillin in one study and both nafcillin and cloxacillin in one study. Detailed characteristics of the included studies are provided in Table 1. Additional information was provided by the authors of five studies [8,9,28–30]. Two studies reported SAB-associated mortality and were analyzed together with the respective outcome analyses [29,30]. SAB-associated mortality was not specifically defined in the respective studies. There was no difference in the proportion of patients with abscesses in all studies (RR of 0.92 (0.64, 1.33)). The proportion of patients with endocarditis in all studies was lower in the cefazolin than in the ASP treatment group (RR of 0.68 (0.55, 0.85), Supplementary Fig. S1).

Assessment of bias within studies

The quality of the individual studies was assessed using the NOS score [18] (Supplementary Table 3). None of the studies reached the maximum score of nine. Regarding the criterion ‘Selection’, all but three studies obtained 4/4 points [31–33]. Regarding the criterion ‘Comparability’, only two studies received 2/2 stars [9,29] as they had performed propensity score matching. Three studies received no stars due to relevant imbalances of the cohorts [32–34]. Regarding the criterion ‘Outcome’, none of the studies received 3/3 stars mostly because the adequacy of the follow-up of cohorts was judged to be insufficient, as patients lost to follow-up were not reported.

---

Fig. 1. PRISMA flow diagram of study identification and selection process for outcome analysis 431 (modified from Moher and colleagues) [42].
### 90-day all-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Cefazolin Events</th>
<th>ASP Events</th>
<th>Total Events</th>
<th>Relative Risk</th>
<th>RR 95%−CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai 2015</td>
<td>21 105</td>
<td>75 249</td>
<td>96 354</td>
<td>0.66</td>
<td>[0.43; 1.02]</td>
<td>23.3%</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>1 41</td>
<td>5 41</td>
<td>6 82</td>
<td>0.20</td>
<td>[0.02; 1.64]</td>
<td>2.7%</td>
</tr>
<tr>
<td>Lee 2018</td>
<td>2 79</td>
<td>24 153</td>
<td>26 179</td>
<td>0.17</td>
<td>[0.04; 0.71]</td>
<td>5.4%</td>
</tr>
<tr>
<td>Li 2014</td>
<td>0 59</td>
<td>1 34</td>
<td>1 93</td>
<td>0.19</td>
<td>[0.01; 4.62]</td>
<td>1.2%</td>
</tr>
<tr>
<td>McDanel 2017</td>
<td>231 1163</td>
<td>502 2004</td>
<td>733 2567</td>
<td>0.79</td>
<td>[0.69; 0.91]</td>
<td>33.0%</td>
</tr>
<tr>
<td>Paul 2011</td>
<td>29 72</td>
<td>91 281</td>
<td>120 363</td>
<td>1.24</td>
<td>[0.90; 1.73]</td>
<td>26.9%</td>
</tr>
<tr>
<td>Pollett 2011</td>
<td>5 70</td>
<td>5 30</td>
<td>10 100</td>
<td>0.43</td>
<td>[0.13; 1.37]</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

Random effects model: 289 1589; 703 2802; 0.71 [0.50; 1.02] 100.0%

Heterogeneity: $I^2 = 63\%$, $\tau^2 = 0.0967$, $p = 0.01$

Favours Cefazolin Favours ASP

### 30-day all-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Cefazolin Events</th>
<th>ASP Events</th>
<th>Total Events</th>
<th>Relative Risk</th>
<th>RR 95%−CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai 2015</td>
<td>11 105</td>
<td>62 249</td>
<td>73 354</td>
<td>0.42</td>
<td>[0.23; 0.77]</td>
<td>13.2%</td>
</tr>
<tr>
<td>Davis 2018</td>
<td>83 793</td>
<td>731 6520</td>
<td>814 7253</td>
<td>0.93</td>
<td>[0.75; 1.16]</td>
<td>33.0%</td>
</tr>
<tr>
<td>Flynt 2017</td>
<td>4 68</td>
<td>4 81</td>
<td>8 149</td>
<td>1.19</td>
<td>[0.31; 4.59]</td>
<td>3.5%</td>
</tr>
<tr>
<td>Kimmig 2018</td>
<td>8 61</td>
<td>20 131</td>
<td>28 262</td>
<td>0.86</td>
<td>[0.40; 1.84]</td>
<td>9.3%</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>2 41</td>
<td>2 41</td>
<td>4 82</td>
<td>1.00</td>
<td>[0.15; 6.76]</td>
<td>1.8%</td>
</tr>
<tr>
<td>Lee 2018</td>
<td>2 79</td>
<td>13 163</td>
<td>15 182</td>
<td>0.32</td>
<td>[0.07; 1.37]</td>
<td>3.0%</td>
</tr>
<tr>
<td>Li 2014</td>
<td>0 59</td>
<td>1 34</td>
<td>1 93</td>
<td>0.19</td>
<td>[0.01; 4.62]</td>
<td>0.7%</td>
</tr>
<tr>
<td>McDanel 2017</td>
<td>113 1163</td>
<td>307 2004</td>
<td>420 4177</td>
<td>0.63</td>
<td>[0.52; 0.78]</td>
<td>33.8%</td>
</tr>
<tr>
<td>Monogue 2018</td>
<td>0 71</td>
<td>3 71</td>
<td>3 74</td>
<td>0.14</td>
<td>[0.01; 2.72]</td>
<td>0.8%</td>
</tr>
<tr>
<td>Renaud 2011</td>
<td>1 14</td>
<td>1 13</td>
<td>2 27</td>
<td>0.93</td>
<td>[0.06; 13.37]</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Random effects model: 224 2453; 1144 9307; 0.70 [0.54; 0.91] 100.0%

Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0424$, $p = 0.12$

Favours Cefazolin Favours ASP

### Treatment failure / relapse

<table>
<thead>
<tr>
<th>Study</th>
<th>Cefazolin Events</th>
<th>ASP Events</th>
<th>Total Events</th>
<th>Relative Risk</th>
<th>RR 95%−CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai 2015</td>
<td>6 105</td>
<td>4 249</td>
<td>10 354</td>
<td>3.56</td>
<td>[1.02; 12.35]</td>
<td>6.0%</td>
</tr>
<tr>
<td>Flynt 2017</td>
<td>12 68</td>
<td>11 81</td>
<td>23 151</td>
<td>1.30</td>
<td>[0.61; 2.76]</td>
<td>11.7%</td>
</tr>
<tr>
<td>Kimmig 2018</td>
<td>4 61</td>
<td>10 131</td>
<td>14 192</td>
<td>0.86</td>
<td>[0.28; 2.63]</td>
<td>7.0%</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>6 41</td>
<td>6 41</td>
<td>12 82</td>
<td>1.00</td>
<td>[0.35; 2.84]</td>
<td>7.7%</td>
</tr>
<tr>
<td>Lee 2018*</td>
<td>24 79</td>
<td>82 163</td>
<td>106 242</td>
<td>0.60</td>
<td>[0.42; 0.87]</td>
<td>20.2%</td>
</tr>
<tr>
<td>Li 2014</td>
<td>14 59</td>
<td>16 34</td>
<td>30 93</td>
<td>0.50</td>
<td>[0.28; 0.90]</td>
<td>15.0%</td>
</tr>
<tr>
<td>McDanel 2015</td>
<td>20 1163</td>
<td>28 2004</td>
<td>48 3167</td>
<td>1.23</td>
<td>[0.70; 2.17]</td>
<td>15.3%</td>
</tr>
<tr>
<td>Monogue 2018</td>
<td>6 71</td>
<td>8 71</td>
<td>14 142</td>
<td>0.75</td>
<td>[0.27; 2.05]</td>
<td>8.1%</td>
</tr>
<tr>
<td>Rao 2015</td>
<td>6 103</td>
<td>7 58</td>
<td>13 161</td>
<td>0.48</td>
<td>[0.17; 1.37]</td>
<td>7.7%</td>
</tr>
<tr>
<td>Renaud 2011</td>
<td>0 14</td>
<td>2 13</td>
<td>2 27</td>
<td>0.19</td>
<td>[0.01; 3.54]</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Random effects model: 98 1764; 174 2845; 0.84 [0.59; 1.18] 100.0%

Heterogeneity: $I^2 = 44\%$, $\tau^2 = 0.1189$, $p = 0.06$

Favours Cefazolin Favours ASP

### Nephrotoxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Cefazolin Events</th>
<th>ASP Events</th>
<th>Total Events</th>
<th>Relative Risk</th>
<th>RR 95%−CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flynt 2017</td>
<td>9 68</td>
<td>26 81</td>
<td>35 109</td>
<td>0.41</td>
<td>[0.21; 0.82]</td>
<td>54.3%</td>
</tr>
<tr>
<td>Lee 2018</td>
<td>1 79</td>
<td>1 79</td>
<td>2 158</td>
<td>1.00</td>
<td>[0.06; 15.71]</td>
<td>3.4%</td>
</tr>
<tr>
<td>Li 2014</td>
<td>0 59</td>
<td>1 34</td>
<td>1 93</td>
<td>0.19</td>
<td>[0.01; 4.62]</td>
<td>2.5%</td>
</tr>
<tr>
<td>Monogue 2018</td>
<td>2 71</td>
<td>12 71</td>
<td>14 142</td>
<td>0.17</td>
<td>[0.04; 0.72]</td>
<td>12.0%</td>
</tr>
<tr>
<td>Rao 2015</td>
<td>1 103</td>
<td>0 58</td>
<td>1 161</td>
<td>1.70</td>
<td>[0.07; 40.96]</td>
<td>2.5%</td>
</tr>
<tr>
<td>Youngster 2014</td>
<td>4 119</td>
<td>42 366</td>
<td>46 375</td>
<td>0.29</td>
<td>[0.11; 0.80]</td>
<td>25.3%</td>
</tr>
</tbody>
</table>

Random effects model: 17 499; 82 689; 0.36 [0.21; 0.59] 100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.70$

Favours Cefazolin Favours ASP

---

Fig. 2. Results for the primary and the secondary endpoints in patients with *Staphylococcus aureus* bacteraemia. ASP, anti-staphylococcal penicillins; CI, confidence interval; RR, relative risk. * Data from propensity matched cohort only.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of participants (studies)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality of the evidence (GRADE)</th>
<th>Events in cefazolin group (95% CI)</th>
<th>Events in ASP group (95% CI)</th>
<th>Relative risk</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day all-cause mortality</td>
<td>11 760 (10)</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>All plausible residual confounding would reduce the demonstrated effect</td>
<td>Very low</td>
<td>1144/9307 (12.3%)</td>
<td>224/2453 (9.1%)</td>
<td><strong>0.70</strong> (0.54, 0.91)</td>
<td>123 per 1.000</td>
</tr>
<tr>
<td>90-day all-cause mortality</td>
<td>4391 (7)</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>All plausible residual confounding would reduce the demonstrated effect</td>
<td>Very low</td>
<td>703/2802 (25.1%)</td>
<td>289/1589 (18.2%)</td>
<td><strong>0.71</strong> (0.50, 1.02)</td>
<td>251 per 1.000</td>
</tr>
<tr>
<td>Treatment failure/relapse</td>
<td>4609 (10)</td>
<td>Serious</td>
<td>Not serious</td>
<td>Serious ²</td>
<td>Serious ²</td>
<td>All plausible residual confounding would reduce the demonstrated effect</td>
<td>Very low</td>
<td>174/2845 (6.1%)</td>
<td>98/1764 (5.6%)</td>
<td><strong>0.84</strong> (0.59, 1.18)</td>
<td>61 per 1.000</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>1188 (6)</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious ²</td>
<td>All plausible residual confounding would reduce the demonstrated effect</td>
<td>Very low</td>
<td>84/689 (12.2%)</td>
<td>15/501 (3.4%)</td>
<td><strong>0.35</strong> (0.21, 0.57)</td>
<td>122 per 1.000</td>
</tr>
</tbody>
</table>

Adapted from GRADE Working Group grades of evidence. Calculations of anticipated risk using GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org. ASP, anti-staphylococcal penicillin; CI, confidence interval; RR, relative risk. HIGH: We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change our confidence in the estimate of effect. MODERATE: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. LOW: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. VERY LOW: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. Each issue judged as bearing of serious meaning resulted in the assessed features were had a serious risk quality of evidence was downgraded by one.

1 Inconsistency (heterogeneity) was judged to be not serious when heterogeneity was low or moderate.
2 Judged as serious due to the imprecise and inconsistent definitions among studies.
3 Quality of evidence was up-graded due to the strong and consistent observed effect.
**Primary endpoint: 90-day all-cause mortality**

For the primary endpoint 90-day all-cause mortality, data from seven studies comprising 4391 patients were extracted (Fig. 2(a)). Pooling these results, we observed an overall 90-day mortality of 25.1% (703/2,802) in the ASP group and 18.2% (289/1,589) in the cefazolin group, resulting in an RR of 0.71, 95% CI (0.50, 1.02)). There was moderate heterogeneity in the studies reporting the primary endpoint (I² = 63%, p = 0.01). Cefazolin may therefore not be associated with increased 90-day mortality (low-quality evidence).

**Secondary endpoints**

For the secondary endpoints, we identified 10 studies reporting 30-day all-cause mortality with 11760 patients (Fig. 2(b)), 10 studies reporting on treatment failure/relapse (4609 patients; Fig. 2(c)) and six studies reporting on nephrotoxicity (1188 patients; Fig. 2(d)). Pooling these studies, cefazolin treatment may be associated with lower 30-day mortality rates (low-quality evidence, RR 0.70 (0.54, 0.91)) and less nephrotoxicity (low-quality evidence, RR 0.36 (0.21, 0.59)). We are uncertain whether cefazolin and ASP differ regarding treatment failure/relapse as the quality of evidence has been assessed as very low, RR of 0.84 (0.59, 1.18)). We are uncertain whether cefazolin may be associated with increased 30-day mortality (low-quality evidence, RR 0.70 (0.54, 0.91)) and less nephrotoxicity (low-quality evidence, RR 0.36 (0.21, 0.59)).

**Assessment of bias across studies**

Funnel plots revealed no evidence of publication bias, particularly for those studies reporting 30-day all-cause mortality (Supplementary Fig. S2). However, the small number of considered studies hampered the assessment. According to the GRADE classification, we judged the certainty of evidence to be low mainly due to the inherent high risk of bias introduced by retrospective, non-randomized trial designs (Table 2). In particular, an indication bias could not be ruled out, which could possibly overestimate the favourable treatment effect of cefazolin compared to ASPs.

**Sensitivity and subgroup analyses**

The results of the sensitivity analyses supported the main conclusions. Considering the different effect measures (RR versus OR), the results were relatively robust (Supplementary Table S4). In the leave-one-out cross-validation, we observed that the direction of the pooled point estimates was relatively robust (Supplementary Table S5).

For the subgroup analysis of infections with potential high pathogen inoculum, we identified three studies reporting on 90-day all-cause mortality (42 patients with endocarditis, Fig. 3(a);
46 patients with abscesses, Fig. 4(a)) and six studies reporting on 30-day all-cause mortality (652 patients with endocarditis, Fig. 3(b); 273 patients with abscesses, Fig. 4(b)). There was no association of treatments with 90-day all-cause mortality (endocarditis: RR of 0.71 (0.12, 4.05); abscesses: RR of 0.71 (0.37, 1.34); abscesses: RR of 0.76 (0.25, 2.28)). Heterogeneity for studies reporting on endocarditis and abscesses was low ($I^2 = 0–7\%$).

In the subgroup analyses only comprising studies comparing cefazolin and nafcillin, we identified five studies reporting on the primary outcome (1425 patients with cefazolin; 2519 patients with nafcillin; Supplementary Fig. S3). The RR for 90-day all-cause mortality was 0.70 (0.43, 1.14), for 30-day all-cause mortality 0.63 (0.52, 0.77), for treatment failure/relapse 0.89 (0.61, 1.29) and for nephrotoxicity 0.37 (0.20, 0.67) (Supplementary Fig. S3). There were only two studies applying propensity score matching that reported crude numbers and both studies were conducted by the same study group [8,29]. We did not perform a specific analysis for this subset.

**Discussion**

With this systematic review, we aimed to summarize the current evidence for the choice of cefazolin vs. ASP for patients with methicillin-sensitive SAB. Our literature search identified only non-randomized cohort studies with inherent high risk of bias. Meta-analysis of the available data demonstrates that treatment with cefazolin was not associated with increased 90-day mortality and associated with a better outcome with regard to the chosen secondary outcomes (i.e. 30-day mortality and nephrotoxicity) as compared to treatment with ASP. A subgroup analysis with patients with potentially high pathogen load, i.e. endocarditis and abscesses, was inconclusive as only two studies reported on these outcome parameters.

The main limitation of our systematic review was that all available evidence was derived from non-randomized, largely single-centre studies with an inherent high risk of bias. In particular, an attrition bias could potentially lead to an underestimation of the cefazolin inoculum effect. The clinical studies were not designed to assess the subgroups of patients with presumed high bacterial load, specifically there were no studies focusing on patients with endocarditis or abscesses. In addition, our search strategy did not specifically include manual searches for unpublished studies other than conference proceedings that are covered by the utilized electronic databases. However, we asked contacted authors whether they were aware of any unpublished or ongoing studies. Our analysis that includes data from over 11,000 patients reveals a relative consistency of the direction of the studies, i.e. to

![Fig. 4. Results of the assessment of the impact of a potential inoculum effect in patients with Staphylococcus aureus bacteraemia with abscesses. ASP, anti-staphylococcal penicillins; CI, confidence interval; RR, relative risk.](image-url)
favour cefazolin treatment. To compensate for the heterogeneity of included studies, we performed random-effects meta-analyses and several sensitivity analyses which supported our main conclusions. Of note, rates of endocarditis (cefazolin: 151/2523, 6%, ASP: 780/9337, 8.3%) were different between the groups of patients treated with cefazolin vs. ASP considering all studies. Given the observational nature of the studies, it more likely reflects the treating physician choice of treatment contributing to a potential indication bias. A further limitation was that two studies reporting only SAB-associated mortality rates were nevertheless included in our meta-analysis as the risk of bias and the inter-study variation was already high and we did not want to ignore two valuable studies. This systematic review provides evidence that cefazolin treatment is associated with decreased rates of nephrotoxicity as compared with ASP. An indication bias — i.e. that sicker patients with increased risk of renal failure were treated with ASPs, as this has been suggested to be the treatment of choice — must be taken into consideration. In this context, age, co-morbidities and poly-pharmacy, common among the elderly, increase the risk for idiosyncratic drug toxicity of ASP [35,36].

Of note, three systematic reviews comparing cefazolin vs. ASP have been published in 2018 [37–39]. All three systematic reviews showed an association between lower mortality rates for cefazolin treatment compared with ASP treatment. The main difference and reason why we decided to perform this analysis, nevertheless, is that we identified more studies and more importantly twice as many patients. Also, one main difference to previous systematic reviews is that we performed subgroup analysis on patients with cefazolin vs. nafcillin and with endocarditis and abscesses. Furthermore, our analysis included also non-published additional data, which were requested from and made available by authors from the underlying cohort studies.

Exemplarily, in the most recent systematic review on this topic [39] four studies reported here were not included into the meta-analysis [8,27,30,40]. Also, we are stricter in reporting the outcome parameters. The primary outcome in their study was mortality. Therefore, the authors combined all available mortality data from the included studies in one variable, irrespective of assessed time points (e.g. hospital mortality vs. 30- or 90-day mortality) while we differentiated between the different follow-up periods.

**Outweighing the inoculum effect against toxicity**

Ranking cefazolin as an alternative agent to ASP only reflects concerns about a possible inactivation of cefazolin at the site of infection with the consequence of therapeutic failures. Most reports of clinical failure with cefazolin are case reports or case series and are limited by a small sample size and possible selection bias [12,13]. Only Lee et al. recently could demonstrate a higher treatment failure outcome whether being treated with cefazolin or ASP considering all studies. Given the retrospective design of the available data with the inherent high risk of indication bias, no firm conclusion regarding the pre-specified outcomes can be drawn. Multicentre, randomized controlled studies are required to definitively identify the safest and most effective treatment option for patients with SAB.

**Conclusions**

Combined retrospective observational data from over 11000 patients from four continents suggests that cefazolin is at least as effective as ASPs for SAB, and is associated with less nephrotoxicity. However, given the retrospective design of the available data with the inherent high risk of indication bias, no firm conclusion regarding the pre-specified outcomes can be drawn. Multicentre, randomized controlled studies are required to definitively identify the safest and most effective treatment option for patients with SAB.

**Transparency declaration**

S.H. received speaker’s fees from Pfizer, MSD and Astra Zeneca. M.P. has participated in international advisory boards for Pfizer, Novartis, Basilea and Cubist and received speaker’s fees from the same companies. S.W. received speaker’s fees from MSD and InfectoPharm. All other co-authors do not report any conflict of interest.

**Author contributions**

S.W. formulated the hypothesis, performed the systematic analysis and data extraction and drafted the manuscript. S.H. independently performed the systematic analysis and data extraction and wrote the manuscript. M.K. performed the statistical analyses and wrote parts of the manuscript. J.S.D., A.M. and S.L. re-analysed the published study data and wrote part of the manuscript. AS supervised the statistical analyses and reviewed the manuscript. M.W.P. wrote the manuscript and provided the scientific background.

**Acknowledgements**

S.H., M.W.P., S.W., M.K. and A.S. are funded by the German Ministry of Education and Research (BMBF; grant 01EO1502) via the Jena Center of Sepsis Control and Care; S.H., M.W.P. and A.S. are also funded by BMBF grant 01ZZ1803C. We thank all authors of the primary studies for their kind replies. In addition, we thank Dr. Marguerite Monogue for providing additional data and critical appraisal of the manuscript. We thank Dr. Anthony D. Bai for his helpful suggestions.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.03.010.

**References**


