
Charles Darwin University

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

Weis, S.; Kesselmeier, M.; Davis, J. S.; Morris, A. M.; Lee, S.; Scherag, A.; Hagel, S.; Pletz, M. W.

Published in:
Clinical Microbiology and Infection

DOI:
[10.1016/j.cmi.2019.03.010](https://doi.org/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):

Weis, S., Kesselmeier, M., Davis, J. S., Morris, A. M., Lee, S., Scherag, A., Hagel, S., & Pletz, M. W. (2019). Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia. *Clinical Microbiology and Infection*, 25(7), 818-827. <https://doi.org/10.1016/j.cmi.2019.03.010>

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.



Systematic review

Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemiaS. Weis^{1,2,3,*}, M. Kesselmeier^{2,4}, J.S. Davis^{5,6}, A.M. Morris⁷, S. Lee⁸, 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, Germany² Center for Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany³ Department of Anesthesiology and Intensive Care, Jena University Hospital, Jena, Germany⁴ Research Group Clinical Epidemiology, CSCC, Jena University Hospital, Jena, Germany⁵ Global and Tropical Health Division, Menzies School of Health Research, Darwin, NT, Australia⁶ Department of Infectious Diseases, John Hunter Hospital, Newcastle, NSW, Australia⁷ Department of Medicine, Division of Infectious Diseases, Sinai Health System, University Health Network, University of Toronto, Canada⁸ Department of Internal Medicine, Pusan National University School of Medicine and Medical Research Institute,

Pusan National University Hospital, Busan, Republic of Korea

⁹ Institute of Medical Statistics, Computer and Data Sciences, Jena University Hospital, Jena, Germany

ARTICLE INFO

Article history:

Received 21 October 2018

Received in revised form

2 March 2019

Accepted 9 March 2019

Available online 27 March 2019

Editor: M. Paul

Keywords:

Anti-staphylococcal penicillins

Antimicrobial therapy

Bacteraemia

Cefazolin

Flucloxacillin

Meta-analysis

Staphylococcus aureus

ABSTRACT

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 I^2 . 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)) or abscesses (RR 1.17 (0.30, 4.63)), 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/>).

* Corresponding author. S. Weis, Institute for Infectious Diseases and Infection Control, Department of Anesthesiology and Intensive Care Medicine, Center for Sepsis Control and Care, Jena University Hospital, Am Klinikum 1, 07747 Jena, Germany. Tel.: +49 3641 932 4650; fax: +49 3641 932 4652.

E-mail address: sebastian.weis@med.uni-jena.de (S. Weis).

† These authors contributed equally to this work.

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 reported on the endpoint treatment failure, while both indicating insufficient treatment, both outcomes were reported together as one. Definitions are provided in [Supplementary Table S1](#). Other toxicities such as hepatitis, phlebitis or cytopenia were not routinely reported and therefore not assessed. In-hospital mortality as reported by some studies was explicitly not assessed as it was considered as less informative given it is known to substantially vary between countries. Studies that reported on this outcome only were not considered.

Information sources and search

MEDLINE, ISI Web of Science (Science Citation Index Expanded) and the Cochrane Database as well as clinicaltrials.gov were searched from inception to 26 June 2018 for clinical studies

reporting outcomes of SAB patients treated with cefazolin or ASPs. The search terms are provided in [Supplementary Table S2](#). Database searches were complemented by screening the reference lists of relevant studies and reviews as well as by directly asking selected experts for studies that they were aware of, but which were not already included in this analysis. Two authors (S.W., S.H.) independently performed the literature search, identified all studies potentially relevant for this review and selected studies that were included. Conflicts over inclusion were resolved through consensus. All study authors were contacted in order to retrieve all additional available data (also concerning missing data).

Data collection process and risk of bias assessment

One author (S.W.) extracted the number of patients and events for both treatment groups (cefazolin or ASP). Results were independently validated by one other author (S.H.). To assess potential heterogeneity of the study populations, we extracted information on study designs and settings as well as summarized patient characteristics. A formal risk assessment of the individual studies was judged independently by two authors (S.W. and S.H.) according to the Newcastle–Ottawa Scale (NOS) ([Supplementary Table S3](#)) [18]. Differences between the judgements were resolved by discussion. The certainty of evidence was assessed using the guidelines of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [19,20].

Synthesis of results

In random-effects meta-analyses, we pooled relative risks (RRs) with 95% confidence intervals (CIs). Studies were pooled according to the Mantel–Haenszel and DerSimonian–Laird methods for within-study and between-study variance, respectively [21–23]. In studies with zero cell frequencies, a continuity correction of 0.5 was used. Statistical heterogeneity was assessed by I^2 statistic. Heterogeneity was judged to be low for I^2 0–40%, moderate for I^2 30–60%, to be substantial for I^2 50–90% and to be considerable for I^2 75–100%. The importance of this measure depends on the magnitude and direction of effects as well as the precision of the estimate (often judged by the corresponding p -value from the Chi-squared test) [24]. Meta-analysis results are presented as forest plots. In addition, funnel plots were inspected to identify potential evidence for publication bias. To assess a possible indication bias in this context, we performed random-effects meta-analyses to compare the proportions of patients with endocarditis and abscesses in the two treatment groups across all studies reporting these data. In sensitivity analyses of the complete data sets, we also calculated the meta-analysis odds ratio (OR), and performed a leave-one-out cross-validation. We report point estimates and the corresponding 95% CIs. All analyses were performed with R (version 3.4.3 and 3.5.1; R package meta, version 4.9-0) [25,26]. Subgroup analysis was performed for patients with endocarditis or abscesses which are suggested to be 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

Study	Design	Country	No. of centres	Study period	Treatment comparison: cefazolin vs.	Primary endpoint	Secondary endpoints	Sample size
Bai et al., 2015 [28]	Retrospective, non-randomized, propensity score matched cohort study	Canada	6	04/2007–03/2010	Cloxacillin	90-d mortality	Relapse	354
Davis et al., 2018 [8]	Retrospective, non-randomized, cohort study	Australia, New Zealand	27	10/2007–09/2013	Flucloxacillin	30-d mortality, LOS	Admission to intensive care unit, 7-d mortality, LOS	7312
Flynt et al., 2017 [43]	Retrospective, non-randomized, cohort study	USA	4	11/2013–10/2015	Nafcillin	Acute kidney injury	30-d mortality, 60-d recurrence, microbiological failure, LOS, costs	149
Kimmig et al. 2018 [27]	Retrospective, non-randomized cohort study	Germany	1	12/2012–08/2015	Flucloxacillin	In-hospital mortality	Relapse, hospital re-admission, complications, acute renal failure with vancomycin therapy, organ failure	192 in the subgroup of patients treated with cefazolin and flucloxacillin, 297 in total
Lee et al., 2011 [29]	Retrospective, non-randomized, propensity score matched cohort study	Korea	1	01/2004-06/2009	Nafcillin	Treatment failure 4 and 12 weeks	Survival 4 weeks and 12 weeks, interruption to adverse drug events, mean time to defervescence	82
Lee et al., 2018 [9]	Prospective, non-randomized observational cohort study	Korea	10	09/2013–03/2015	Nafcillin	Treatment failure	Mortality	242
Li et al., 2014 [31]	Retrospective, non-randomized cohort study	USA	2	01/2008–06/2012	Oxacillin	Clinical cure at the end of treatment	Treatment failure, 30-, 90-d mortality, adverse events, acute kidney injury	93
McDanel et al., 2017 [44]	Retrospective, non-randomized cohort study	USA	119	2003–2010	Nafcillin/Oxacillin	30-d mortality, 90-d mortality	Recurrence up to 1 year	3167
Monogue et al. 2018 [30]	Retrospective, non-randomized cohort study	USA	1	11/2011–08/2014	Nafcillin	Treatment failure	Adverse drug events	142
Paul et al., 2011 [32]	Retrospective, non-randomized cohort study	Israel	1	1988–1994 1999–2007	Cloxacillin	30-d mortality for empiric treatment; 90-d mortality for definitive treatment	—	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
Pollet et al., 2016 [34]	Retrospective, non-randomized cohort study	USA	1	01/2008–07/2013	Nafcillin	90-d mortality	—	100
Rao et al., 2015 [45]	Retrospective, non-randomized cohort study	USA	2	01/2010–04/2013	Oxacillin	Treatment failure	All cause in hospital mortality, adverse events (including kidney injury), duration of bacteraemia	161
Renaud et al., 2011 [33]	Retrospective, non-randomized cohort study (historical cohort)	Singapore	1	06/2009–12/2009	Cloxacillin	30-d mortality and recrudescence	Length of hospital stay, hospitalization costs, adverse drug reactions	27
Youngster et al. 2014 [40]	Retrospective, non-randomized cohort study	USA	1	2007–2011	Nafcillin	Premature antimicrobial discontinuation	Rates of drug-emergent events	485

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.

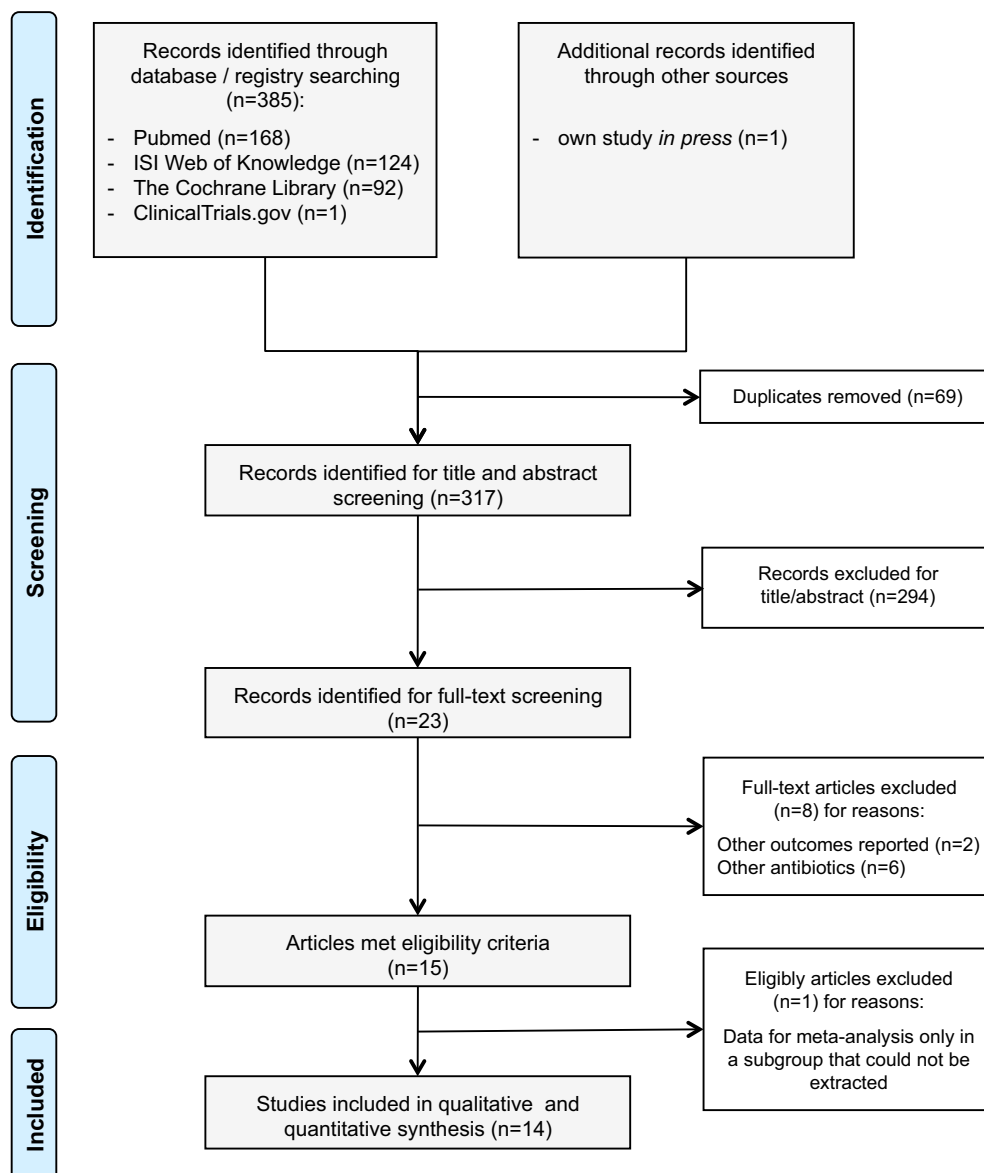


Fig. 1. PRISMA flow diagram of study identification and selection process for outcome analysis 431 (modified from Moher and colleagues) [42].

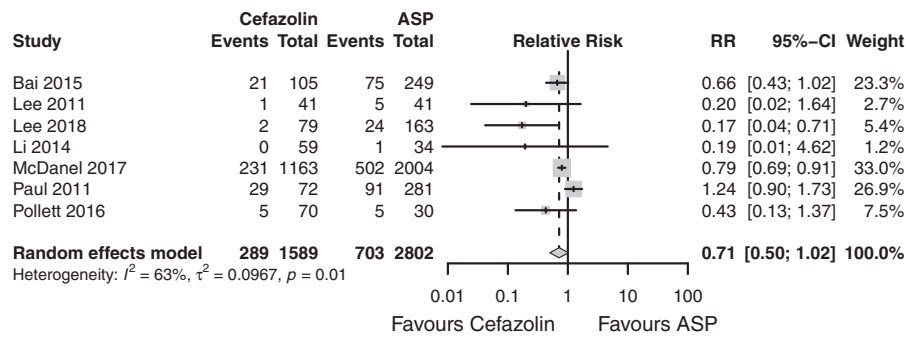
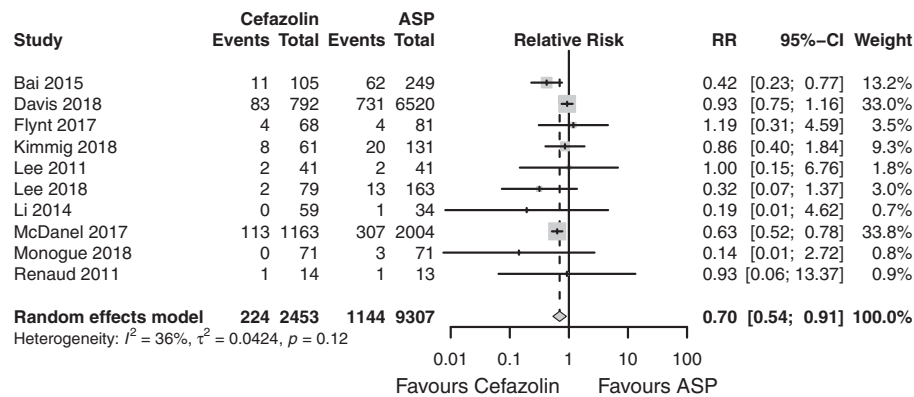
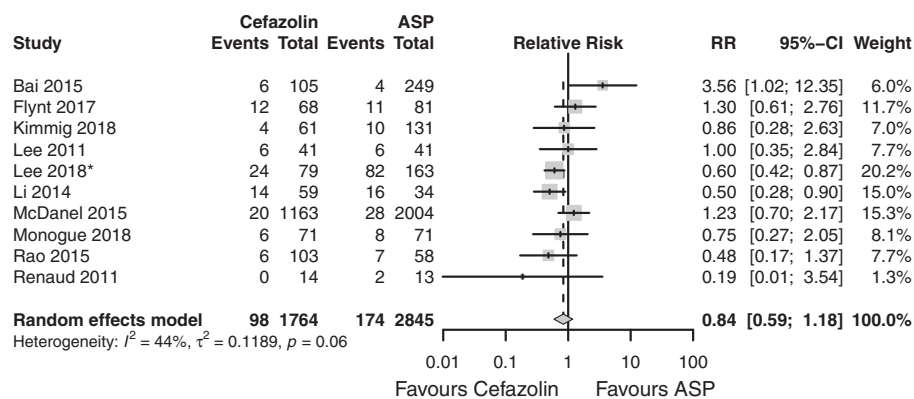
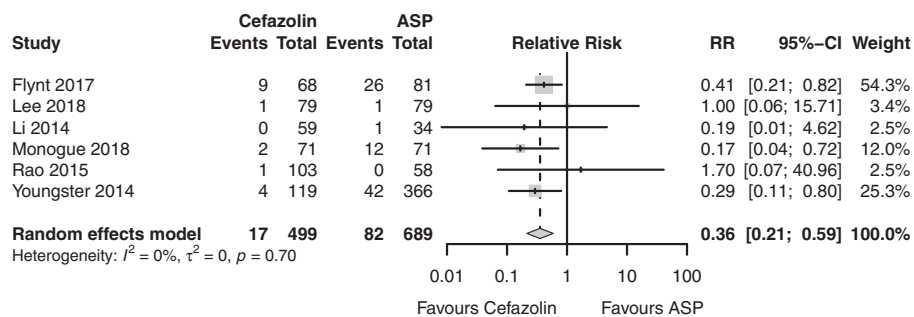
(a) 90-day all-cause mortality**(b) 30-day all-cause mortality****(c) Treatment failure / relapse****(d) Nephrotoxicity**

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 2
GRADE classification of main outcomes considering the different studies that contributed to the compiled effect estimate

Outcome	No. of participants (studies)	Risk of bias	Inconsistency ¹	Indirectness	Imprecision	Other considerations	Quality of the evidence (GRADE)	Events in cefazolin group	Events in ASP group	Relative risk (95% CI)	Anticipated absolute effects	
											Risk with cefazolin treatment	Risk difference with ASP treatment (95% CI)
30-day all-cause mortality	11 760 (10)	Serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕○○ LOW	1144/9307 (12.3%)	224/2453 (9.1%)	0.70 (0.54, 0.91)	123 per 1.000	37 fewer per 1.000 (from 11 fewer to 57 fewer)
90-day all-cause mortality	4391 (7)	Serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕○○ LOW	703/2802 (25.1%)	289/1589 (18.2%)	0.71 (0.50, 1.02)	251 per 1.000	73 fewer per 1.000 (from 5 more to 125 fewer)
Treatment failure/relapse	4609 (10)	Serious	Not serious	Serious ²	Serious ²	All plausible residual confounding would reduce the demonstrated effect	⊕○○○ VERY LOW	174/2845 (6.1%)	98/1764 (5.6%)	0.84 (0.59, 1.18)	61 per 1.000	10 fewer per 1.000 (from 11 more to 25 fewer)
Nephrotoxicity	1188 (6)	Serious	Not serious	Not serious	Serious ²	All plausible residual confounding would reduce the demonstrated effect	⊕⊕○○ ³ LOW	84/689 (12.2%)	15/501 (3.4%)	0.35 (0.21, 0.57)	122 per 1.000	79 fewer per 1.000 (from 52 fewer to 96 fewer)

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 gradepr.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 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 ($I^2 = 63\%$, $p = 0.01$). 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 11 760 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 the evidence has been assessed as very low, RR of 0.84 (0.59, 1.18)). Heterogeneity was low for the endpoints of 30-day all-cause mortality ($I^2 = 36\%$, $p = 0.12$) and nephrotoxicity ($I^2 = 0\%$, $p = 0.70$) and moderate for treatment failure/relapse ($I^2 = 44\%$, $p = 0.06$). Notably, separate analyses for patients with a treatment failure and those

with relapse were not possible due to the overlapping definitions of relapse and treatment failure in some of the considered studies (Supplementary Table S2).

Assessment of bias across studies

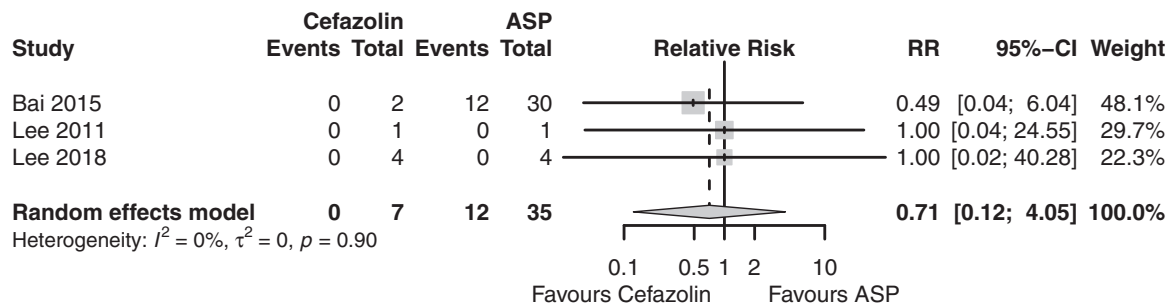
Funnel plots revealed no evidence of publication bias, particularly for those studies reporting 30-day all-cause mortality (Supplementary Fig. S2). However, the small number of considered studies hampered the assessment. According to the GRADE classification, we judged the certainty of evidence to be 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);

(a) 90-day all-cause mortality in patients with endocarditis



(b) 30-day all-cause mortality in patients with endocarditis

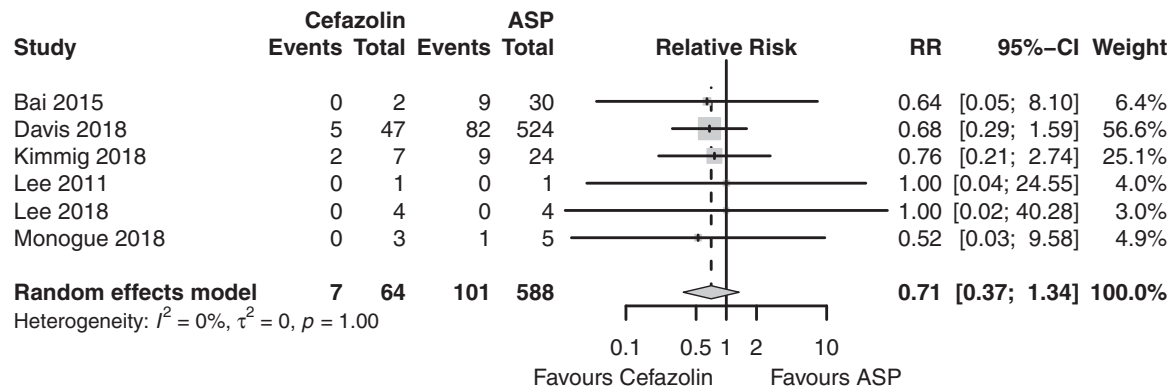


Fig. 3. Results of the assessment of the impact of a potential inoculum effect in patients with *Staphylococcus aureus* bacteraemia with endocarditis. ASP, anti-staphylococcal penicillins; CI, confidence interval; RR, relative risk.

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 1.17 (0.30, 4.63)), for 30-day all-cause mortality (endocarditis: 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.

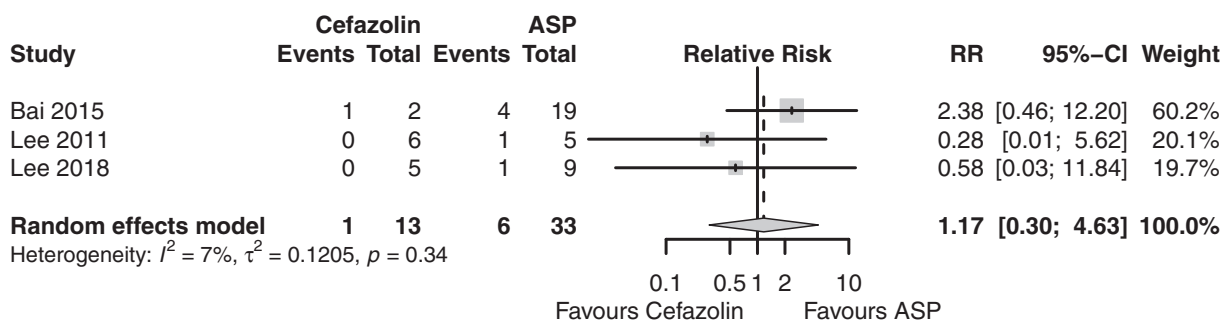
Discussion

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

(a) 90-day all-cause mortality in patients with abscesses



(b) 30-day all-cause mortality in patients with abscesses

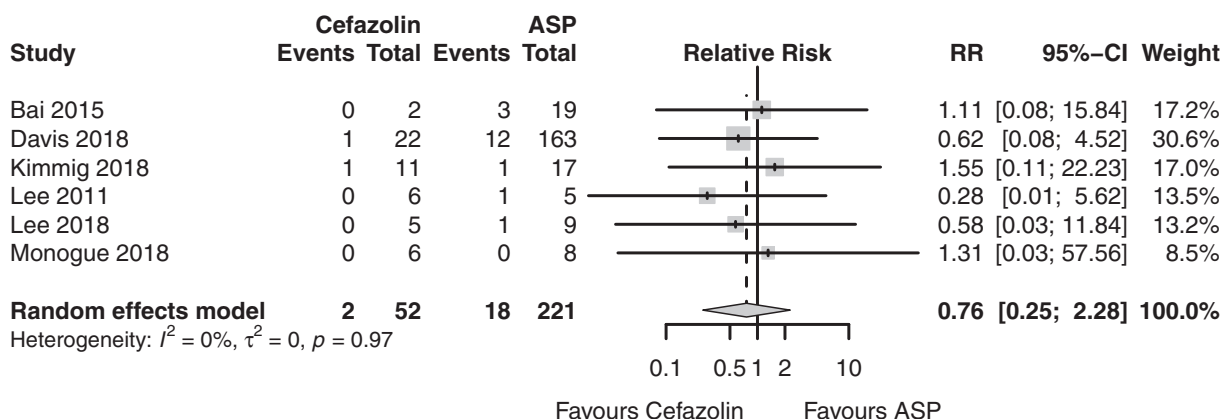


Fig. 4. Results of the assessment of the impact of a potential inoculum effect in patients with *Staphylococcus aureus* bacteraemia with abscesses. ASP, anti-staphylococcal penicillins; CI, confidence interval; RR, relative risk.

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 and 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 and mortality rate in patients infected with organisms that exhibit a cefazolin inoculum effect [9]. In addition, there is an ongoing debate regarding whether the inoculum effect may be an artefact of current susceptibility testing methods rather than a clinically relevant entity because it likely does not represent true pharmacokinetics and pharmacodynamics exposures seen in clinical settings when repeated dosing regimens are administered [41]. At least in our systematic review, cefazolin treatment was not associated with increased mortality as compared to treatment with ASP in the outcome of patients with potential high pathogen load, i.e. patients with endocarditis or abscesses did not show difference in the outcome whether being treated with cefazolin or ASP. Therefore, clinicians should outweigh the risk of an inoculum effect in patients with potential high pathogen load, for which there is sparse clinical evidence against the clinically well-confirmed risk of ASP associated toxicity, particularly in the presence of predisposing factors.

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

- [1] Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler Jr VG. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev* 2015;28:603–61.
- [2] Seifert H, Abele-Horn M, Fätkenheuer G, Glück T, Jansen B, Kern WV, et al. Blutkulturdiagnostik: Sepsis, Endokarditis, Katheterinfektionen. In: Podbielski A, Herrmann M, Kniehl E, Mauch H, Russmann H, editors. *Mikrobiologisch-infektiologische Qualitätsstandards (MiQ)*. München, Germany: Elsevier; 2007.
- [3] Laupland KB, Lyytikäinen O, Sogaard M, Kennedy KJ, Knudsen JD, Ostergaard C, et al. International bacteremia surveillance collaborative, The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study. *Clin Microbiol Infect* 2013;19:465–71.
- [4] Chang FY, Peacock Jr JE, Musher DM, Triplett P, MacDonald BB, Mylotte JM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine* 2003;82:333–9.
- [5] Lopez-Cortes LE, Del Toro MD, Galvez-Acebal J, Bereciartua-Bastarrica E, Farinas MC, Sanz-Franco M, et al. Impact of an evidence-based bundle

- intervention in the quality-of-care management and outcome of *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2013;57:1225–33.
- [6] Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, et al. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia: a narrative review. *Clin Microbiol Infect* 2017;23:253–9.
- [7] Li J, Echevarria KL, Traugott KA. Beta-Lactam Therapy for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Comparative Review of Cefazolin versus Antistaphylococcal Penicillins. *Pharmacotherapy* 2017;37:346–60.
- [8] Davis JS, Turnidge J, Tong SYC. A large retrospective cohort study of cefazolin compared with flucloxacillin for methicillin-susceptible *Staphylococcus aureus* bacteraemia. *Int J Antimicrob Agents* 2018;52:297–300.
- [9] Lee S, Song KH, Jung SI, Park WB, Lee SH, Kim YS, et al. Korea, Comparative outcomes of cefazolin versus nafcillin for methicillin-susceptible *Staphylococcus aureus* bacteraemia: a prospective multicentre cohort study in Korea. *Clin Microbiol Infect* 2018;24:152–8.
- [10] Brook I. Nocolum effect. *Rev Infect Dis* 1989;11:361–8.
- [11] Baddour LM, Wilson WR, Bayer AS, Fowler Jr VG, Tleyjeh IM, Rybak MJ, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation* 2015;132:1435–86.
- [12] Lee S, Kwon KT, Kim HI, Chang HH, Lee JM, Choe PG, et al. Clinical implications of cefazolin inoculum effect and beta-lactamase type on methicillin-susceptible *Staphylococcus aureus* bacteremia. *Microb Drug Res* 2014;20:568–74.
- [13] Nannini EC, Stryjewski ME, Singh KV, Bourgogne A, Rude TH, Corey GR, et al. Inoculum effect with cefazolin among clinical isolates of methicillin-susceptible *Staphylococcus aureus*: frequency and possible cause of cefazolin treatment failure. *Antimicrob Agents Chemother* 2009;53:3437–41.
- [14] Rincon S, Reyes J, Carvajal LP, Rojas N, Cortes F, Panesso D, et al. Cefazolin high-inoculum effect in methicillin-susceptible *Staphylococcus aureus* from South American hospitals. *J Antimicrob Chemother* 2013;68:2773–8.
- [15] Chong YP, Park SJ, Kim ES, Bang KM, Kim MN, Kim SH, et al. Prevalence of blaZ gene types and the cefazolin inoculum effect among methicillin-susceptible *Staphylococcus aureus* blood isolates and their association with multilocus sequence types and clinical outcome. *Eur J Clin Microbiol Infect Dis* 2015;34:349–55.
- [16] Saeki M, Shinagawa M, Yakuwa Y, Nirasawa S, Sato Y, Yanagihara N, et al. Inoculum effect of high concentrations of methicillin-susceptible *Staphylococcus aureus* on the efficacy of cefazolin and other beta-lactams. *J Infect Chemother* 2018;24:212–5.
- [17] Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *Antimicrob Agents Chemother* 2013;57:2326–32.
- [18] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2008. Access: January 10 2019, Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.html.
- [19] Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726–35.
- [20] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013;66:719–25.
- [21] Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;41:55–68.
- [22] Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* 1986;42:311–23.
- [23] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trial* 1986;7:177–88.
- [24] G.S. Higgins JPT, (Ed), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] The Cochrane collaboration, Available from: <http://www.cochrane-handbook.org>.
- [25] RCoreTeam. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. Vienna, Austria. 2017.
- [26] Schwarzer G. Meta: An R package for meta-analysis. *R News* 2007;7:40–5.
- [27] Kimmig A, Weis S, Hagel S, Forstner C, Kesselmeier M, Pletz M. Infektiologische Konsile bei Patienten mit *Staphylococcus aureus* Bakteriämie – eine retrospektive Beobachtungsstudie am Universitätsklinikum Jena. *Dtsch Med Wochenschr* 2018;143:e2.
- [28] Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, et al. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. *J Antimicrob Chemother* 2015;60:1451–61.
- [29] Lee S, Choe PG, Song KH, Park SW, Kim HB, Kim NJ, et al. Is cefazolin inferior to nafcillin for treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia? *Antimicrob Agents Chemother* 2011;55:5122–6.
- [30] Monogue ML, Ortwine JK, Wei W, Eljaaly K, Bhavan KP. Nafcillin versus cefazolin for the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia. *J Infect Public Health* 2018.
- [31] Li J, Echevarria KL, Hughes DW, Cadena JA, Bowling JE, Lewis JS. Comparison of cefazolin versus oxacillin for treatment of complicated bacteremia caused by methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2014;58:5117–24.
- [32] Paul M, Zemer-Wassercug N, Talker O, Lishtzinsky Y, Lev B, Samra Z, et al. Are all beta-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia? *Clin Microbiol Infect* 2011;17:1581–6.
- [33] Renaud CJ, Lin X, Subramanian S, Fisher DA. High-dose cefazolin on consecutive hemodialysis in anuric patients with *Staphylococcal* bacteremia. *Hemodial Int* 2011;15:63–8.
- [34] Pollett S, Baxi SM, Rutherford GW, Doernberg SB, Bacchetti P, Chambers HF. Cefazolin versus Nafcillin for Methicillin-Sensitive *Staphylococcus aureus* Bloodstream Infection in a California Tertiary Medical Center. *Antimicrob Agents Chemother* 2016;60:4684–9.
- [35] Chalasani N, Bjornsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology* 2010;138:2246–59.
- [36] Eljaaly K, Alshehri S, Erstad BL. Systematic Review and Meta-analysis of the Safety of Antistaphylococcal Penicillins Compared to Cefazolin. *Antimicrob Agents Chemother* 2018;62:e01816–7.
- [37] Bidell MR, Patel N, O'Donnell JN. Optimal treatment of MSSA bacteraemias: a meta-analysis of cefazolin versus antistaphylococcal penicillins. *J Antimicrob Chemother* 2018;73:2643–51.
- [38] Rindone JP, Mellen CK. Meta-analysis of trials comparing cefazolin to anti-staphylococcal penicillins in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia. *Br J Clin Pharmacol* 2018;84:1258–66.
- [39] Shi C, Xiao Y, Zhang Q, Li Q, Wang F, Wu J, et al. Efficacy and safety of cefazolin versus antistaphylococcal penicillins for the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia: a systematic review and meta-analysis. *BMC Infect Dis* 2018;18:508.
- [40] Youngster I, Shenoy ES, Hooper DC, Nelson SB. Comparative Evaluation of the Tolerability of Cefazolin and Nafcillin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Infections in the Outpatient Setting. *Clin Infect Dis* 2014;59:369–75.
- [41] Craig WA, Bhavnani SM, Ambrose PG. The inoculum effect: fact or artifact? *Diagn Microbiol Infect Dis* 2004;50:229–30.
- [42] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6. e1000097.
- [43] Flynt LK, Kenney RM, Zervos MJ, Davis SL. The Safety and Economic Impact of Cefazolin versus Nafcillin for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections. *Infect Dis Ther* 2017;6:225–31.
- [44] McDanel JS, Roghmann MC, Perencevich EN, Ohl ME, Goto M, Livorsi DJ, et al. Comparative Effectiveness of Cefazolin Versus Nafcillin or Oxacillin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Infections Complicated by Bacteremia: A Nationwide Cohort Study. *Clin Infect Dis* 2017;65:100–6.
- [45] Rao SN, Rhodes NJ, Lee BJ, Scheetz MH, Hanson AP, Segreti J, et al. Treatment outcomes with cefazolin versus oxacillin for deep-seated methicillin-susceptible *Staphylococcus aureus* bloodstream infections. *Antimicrob Agents Chemother* 2015;59:5232–8.