Original Article

Re-Appraisal of the Effectiveness and Adverse Reaction between Cefazolin and Anti-Staphylococcal Penicillins for Treating Patients with Methicillin-Sensitive *Staphylococcus aureus* Bacteremia: Comprehensive Meta-analysis and Trial Sequential Analysis

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ABSTRACT

Objectives: Patients with methicillin susceptible *Staphylococcus aureus* bacteremia (MsSaB) are treated by cefazolin (Cfz) or anti-staphylococcal penicillin's (ASPs) as the preference drug, although they may be not equally effective in some clinical scenarios. We performed a comprehensive meta-analysis and trial sequential analysis to assess the updated evidence comparing Cfz with ASPs in patients with MsSaB. **Methods:** We searched the databases including PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and ClinicalTrials.gov from inception to July 2019 for studies investigating the effects of Cfz and ASP in patients with MsSaB. The primary endpoint was the 90-day all-cause mortality rate. **Results:** We included 16 studies with 13847 patients with MsSaB. Nine reports showed that the Cfz group might be associated with lower the 90-day all-cause mortality rate than ASP (odds ratio [OR], 0.675; 95% confidence interval [CI], 0.485–0.938; $p=0.019$, low quality of evidence). In addition, Cfz group might be associated with lower 30-day mortality rate (OR, 0.681; 95% CI, 0.533–0.869; $p=0.002$, low quality of evidence), lower incidence rate of treatment failure/relapse (OR, 0.644; 95% CI, 0.509–0.866; $p=0.002$, low quality of evidence) and less nephrotoxicity than ASP (OR, 0.296; 95% CI, 0.167–0.525; $p<0.001$, low quality of evidence). **Conclusion:** We concluded that Cfz and ASP were at least equally effective in patients with MsSaB according to the all-cause mortality rates and nephrotoxicity. Because of heterogeneity, underlying variance and inadequate information size, these results should be interpreted with caution.

Key words: Meta-analysis, Anti-staphylococcal penicillin, Cefazolin, *Staphylococcus aureus*, Bacteremia.

Key Messages: The overall odds ratios for all-cause mortality showed a significant overall effect of patients with methicillin-sensitive *Staphylococcus aureus* bacteremia in cefazolin group for reducing the risk of 90-day all-cause mortality and lower incidence rate of treatment failure/relapse and less nephrotoxicity compared with that of the anti-staphylococcal penicillin's group.

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INTRODUCTION

Staphylococcus aureus (*S. aureus*) commonly colonizes human skin and can transform into a significant human pathogen.[1] However, *S. aureus* bacteremia is often underestimated[2,3] since the associated mortality rate is 50% and the disease is frequently recurrent if treated inadequately.[2,4,5] However, outcomes of *S. aureus* bacteremia can be improved by facilitating adherence to treatment principles and enhancing appropriate choice of effective antibiotic agents.[6,7] Currently, Jackson *et al.* showed that invasive methicillin susceptible *S. aureus* (MSSA) is a more severe public health problem compared to methicillin-resistant *S. aureus* because public health and infection control prevention efforts merely focused on the prevention of methicillin-resistant *S. aureus*.[8] Both anti-staphylococcal penicillins (ASP)[9] and first-generation cephalosporin[6] are drugs of choice for treating patients with methicillin-sensitive *S. aureus* bacteremia (MsSaB). ASP is often recommended as the first-line therapy for MSSA infections.[10] Meanwhile, the cost, multiple dosing schedule and potential penicillin allergy reaction of ASP make it less ideal than cefazolin (Cfz) for certain patients with MsSaB.[11] However, whether first-generation cephalosporin such as Cfz is as effective as ASPs is controversial.[12-15]

Previous systematic reviews and meta-analysis reported that the Cfz group was associated with lower mortality rates than the ASP group or that Cfz group and the ASP group had similar effectiveness.[16-18] However, ranking Cfz as an alternative choice to ASP reflects potential problems owing to the possible inactivation of Cfz in the case of severe MsSaB such as endocarditis;[19] on the contrary, ASPs is associated with penicillin allergy.[20] A literature review showed that some reports on Cfz treatment failure were case reports and therefore, were limited by the small sample bias and publication bias.[21,22] Moreover, Lee *et al.* reported a high treatment failure and mortality rate in patients with *S. aureus* exhibiting a cefazolin inoculum effect (CIE),[14] although the inoculum effect in clinical settings is controversial.[23] Monogue *et al.* showed that Cfz is an appealing first-line agent for most MSSA bacteremia.[24] Nannini EC *et al.* suggested that MsSaB treated with Cfz may result in high treatment failure rates due to the inoculum effect.[22] Brown KA *et al.* reported that Cfz had a broader antibacterial spectrum and a higher possibility of the selection of multi-resistant bacteria and *Clostridium difficile* than ASPs.[25] On the other hand, Cfz was more convenient for dosing and less nephrotoxic than ASPs.[9] The previous studies compared ASP with Cfz but did not adjust for confounding variables,[22,25] particularly efficacy outcomes. Although few previously published meta-analysis have evaluated the impact of Cfz and ASP on the improvement of all-cause mortality and potential adverse reaction in patients with MsSaB, these studies lack some important information such as adequate information size[15,26-28] and number of patients with penicillin allergy.[20] Moreover, previous conclusions concerning all-cause mortality could have been influenced by the heterogeneity between individual studies and insufficient meta-analysis sample size. Quantification of the required sample size is important to ensure the reliability of the data.[29] Clinicians examined whether Cfz could be recommended in the routine care of patients with MsSaB. Therefore, we performed this meta-analysis for the following reasons. First, we identified three studies that were not included in previous[13,27,30,31] systematic review and meta-analysis studies.[16-18] Second, we performed a trial sequential analysis to report adequate information size which is lacking in previous studies. In addition, the primary outcome in this study is the 90-day mortality rate because patients with MsSaB may have high pathogen load and deep tissue infection. We collected all available data from the included studies to differentiate between the two groups. We aimed to perform a systematic literature review, meta-analysis and trial sequential analysis to compare clinical outcomes between patients with MsSaB receiving ASP and receiving Cfz.

MATERIALS AND METHODS

Search strategy and inclusion criteria

This study was performed according to the Declaration of Helsinki and the protocol was approved by the institutional review board of Changhua Christian Hospital (CCH IRB No. 180801). From the earliest record to July 2019, we searched PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and ClinicalTrials.gov for studies on care bundles for patients with MsSaB. All studies reporting the effects of Cfz versus ASP in patients with MsSaB were eligible for inclusion. Detailed search strategies are presented in Supplementary Table S1.

Definition of study outcomes

The definition of ASP included flucloxacillin, nafcillin, methicillin, dicloxacillin, oxacillin, floxacillin, cloxacillin, and isoxazolylpenicillin. The definition of Cfz was Cfz. We included all trials and studies that provided data on one or more of our target outcomes for both the treated (receiving Cfz) and control groups (receiving ASP). The primary endpoint was defined as 90-day all-cause

Table S1: Complete search strategies.

Search term	Paper number
#1) (((*Staphylococcus aureus*[MeSH Terms]) OR aureus) OR *Staphylococcus aureus*))	124547
#2) (((((blood stream) OR blood) OR septicemia) OR septicemia) OR bacteremia) OR bacteraemia) OR bacteraemia) OR Blutstrom*) OR bakteriamie))	445998
#3) #1 and #2	66665
#4) ((((((((((((((flucloxacillin) OR nafcillin) OR methicillin) OR dicloxacillin) OR oxacillin) OR floxacillin) OR cloxacillin) OR betalactam) OR betala*) OR penicillin) OR beta-la*) OR isoxazolylpenicillin)	124547
# 5) (cefazolin delta-3-methyl ester) or (cefazolin delta-2-methyl ester) or (Cefazolin)	5216
#6) #4 and #5	1868
7) #3 and #6	237

Notes: From the earliest record to July 2019, we searched PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and ClinicalTrials.gov for studies on care bundles for patients with MsSaB. All studies reporting the effects of Cfz versus ASP in patients with MsSaB were eligible for inclusion. Detailed search strategies are presented in this Supplementary Table. The definition of ASP included flucloxacillin, nafcillin, methicillin, dicloxacillin, oxacillin, floxacillin, cloxacillin, and isoxazolylpenicillin. The definition of Cfz was Cfz. We included all trials and studies that provided data on one or more of our target outcomes for both the treated (receiving Cfz) and control groups (receiving ASP). The primary endpoint was defined as 90-day all-cause mortality. Secondary endpoints were defined as three components, including 30-day all-cause mortality, treatment failure/relapse and nephrotoxicity. Because hepatitis, phlebitis or cytopenia were not routinely reported, we only described nephrotoxicity and did not described others

mortality. Secondary endpoints were defined as three components, including 30-day all-cause mortality, treatment failure/relapse and nephrotoxicity. Because hepatitis, phlebitis or cytopenia were not routinely reported, we only described nephrotoxicity and did not described others.

Data extraction and quality assessment

Two reviewers (CHC and YMC) examined all retrieved articles and extracted data using a predetermined form, recording the name of the first author, year of publication, country where the study was conducted, study design (prospective studies or retrospective studies), demographic and disease characteristics of participants, number of enrolled participants and quality assessment of each study. We tried to contact the corresponding authors of the selected articles in order to retrieve some concerning missing data. Each reviewer independently evaluated the quality of the eligible studies, using the Jadad scale for the quasi-experimental studies and Newcastle-Ottawa quality assessment scale for retrospective studies.[32,33] The certainty of evidence was assessed using the previous reports.[34,35] According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification, we listed the certainty of evidence at Supplementary Table S2.

Statistical analysis

The outcome measures were determined by the odds ratios (ORs) and a random effects model with pool individual ORs was used. Analyses were conducted using the Comprehensive Meta-Analysis software version 3.0 (Biostat, NJ, USA). Between-trial heterogeneity was determined using I^2 tests. 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%.And, values > 50% were regarded as considerable heterogeneity.[36] Funnel plots and Egger's test were used to examine potential publication bias. Statistical significance was defined as a p-value < 0.05. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Table S3).[37]

In trial sequential analyses, the inconsistence of heterogeneity (I^2) adjusted by required information size was calculated. According to Hemmingsen,[38] the required information size was calculated with an intervention effect of a 30% relative risk reduction, an overall 5% risk of a type I error and a risk of a type II error of 20%. All trial sequential analyses were performed using TSA version 0.9 beta (www.ctu.dk/tsa) for these analyses.

RESULTS

Eligible studies

Out of 237 potentially eligible studies, we excluded irrelevant studies (Figure 1) and finally, 16 studies with a total of 13847 patients were included in this meta-analysis.[14,26,28,31,39-46] The studies were performed in North America (8 studies), Asia (7 studies) and Europe (1 study). The end points used in these studies varied. The characteristics of the studies fulfilling the inclusion criteria are presented in Table 1. There were 2 and 14 prospective and retrospective studies respectively (Table 1).

Table S2: GRADE classification.

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 /1.000	37/ 1.000 (from 11 to 57)
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 /1.000	73 / 1.000 (from 5 more to 125)
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/ 1.000	10 /1.000 (from 11 more to 25)
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 /1.000	79 / 1.000 (from 52 to 96)

Footnote: GRADE classification of main outcomes considers the different studies that contributed to the compiled effect estimate. We adapted from GRADE Working Group grades of evidence. Calculations of anticipated risk using GRADEpro GDT: GRADEpro Guideline Development Tool. McMaster University, 2015 (developed by Evidence Prime, Inc.).

Abbreviation: ASP, anti-staphylococcal penicillin; CI, confidence interval; RR, relative risk.

Risk assessment: (1)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. (2)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.

Note:

Two reviewers (CHC and YMC) examined all retrieved articles and extracted data using a predetermined form, recording the name of the first author, year of publication, country where the study was conducted, study design (prospective studies or retrospective studies), demographic and disease characteristics of participants, number of enrolled participants and quality assessment of each study. We tried to contact the corresponding authors of the selected articles in order to retrieve some concerning missing data. Each reviewer independently evaluated the quality of the eligible studies, using the Jadad scale[1] for the quasi-experimental studies and Newcastle-Ottawa quality assessment scale[2] for retrospective studies. The certainty of evidence was assessed using the previous reports.[3]

Table 1: Summary of the retrieved trials investigating two groups.

Study	Design	Country	No. of centres	Study period	Treatment comparison: cefazolin vs.	Primary endpoint	Secondary endpoints	Sample size
Renaud *et al.* 2011 [40]	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
Paul *et al.* 2011[39]	Retrospective, non-randomized cohort study	Israel	1	1988–1994; 1999–2007	Cloxacillin	30-d mortality for empiric treatment; 90-d mortality for definitive treatment	—	353
Lee *et al.* 2011 [41]	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
Youngster *et al.* 2014 [26]	Retrospective, non-randomized cohort study	USA	1	2007–2011	Nafcillin	Premature antimicrobial discontinuation	Rates of drug-emergent events	485
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
Rao *et al.* 2015 [42]	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
Bai *et al.* 2015 [43]	Retrospective, non-randomized, propensity score matched cohort study	Canada	6	04/2007–03/2010	Cloxacillin	90-d mortality	Relapse	354
Chong *et al.* 2015[27]	Retrospective, non-randomized cohort study	Korea	1	08/2008-07/2011	Nafcillin	30-d and 12 weeks mortality	Relapse	220
Pollet *et al.* 2016 [28]	Retrospective, non-randomized cohort study	USA	1	01/2008–07/2013	Nafcillin	90-d mortality	—	100
Song *et al.* 2017 [29]	prospective cohort study	Korea	10	09/2013-03/2015	Nafcillin	cefazolin inoculum effect	30-d mortality, 90-d mortality	303

(*Continued*)

Table 1: (*Continued*).

Study	Design	Country	No. of centres	Study period	Treatment comparison: cefazolin vs.	Primary endpoint	Secondary endpoints	Sample size
Flynt *et al.* 2017 [44]	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
McDanel *et al.* 2017 [45]	Retrospective, non-randomized cohort study	USA	119	2003–2010	Nafcillin/ Oxacillin	30-d mortality, 90-d mortality	Recurrence up to 1 year	3167
Kimmig *et al.* 2018 [46]	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	297
Lee *et al.* 2018 [14]	Prospective, non-randomized observational cohort study	Korea	10	09/2013–03/2015	Nafcillin	Treatment failure	Mortality	242
Monogue *et al.* 2018 [24]	Retrospective, non-randomized cohort study	USA	1	11/2011–08/2014	Nafcillin	Treatment failure	Adverse drug events	142
Davis *et al.* 2018 [13]	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

Table S3: PRISMA 2009 Checklist.			
Section/Topic	**#**	**Checklist Item**	**Reported on Page #**
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS).	2-3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Supplementary Material
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Supplementary Material
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review and, if applicable, included in the meta-analysis).	Supplementary Material
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Supplementary Material
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary Material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis.	Supplementary Material
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Supplementary Material
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Supplementary Material
Section/Topic	#	Checklist Item	Reported on Page 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementary Material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Supplementary Material

(*Continued*)

Table S3: (*Continued*).			
Section/Topic	**#**	**Checklist Item**	**Reported on Page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementary Material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Supplementary Material
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3-10
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	3-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	3-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias) and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

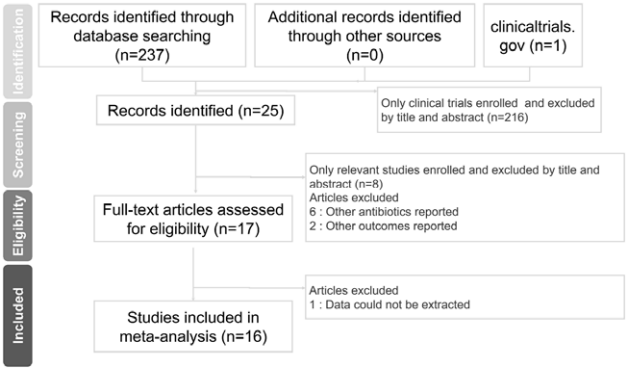

Figure 1: Flow Chart.

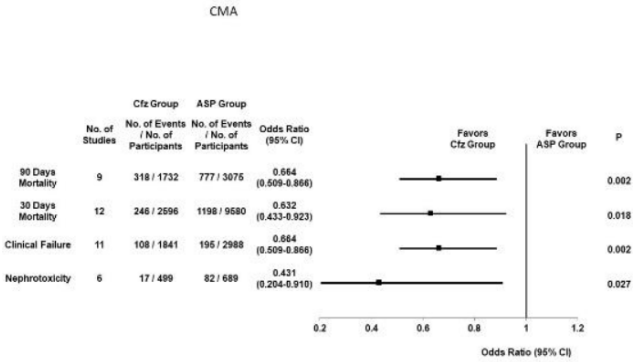

Figure 2: Forest plot of the overall odds ratios for all outcomes between two groups.

Forest plot of the overall odds ratios for all outcomes between two groups. The 90 days all-cause mortality rate was significantly lower in the Cef1 group compared with that in ASP group (OR, 0.675; 95% CI, 0.485-0.938; p = 0.019). The incidence rate of 30 days all-cause mortality was significantly lower in Cef1 group compared with that in ASP group (OR, 0.681; 95% CI, 0.533-0.869; p = 0.002). The incidence rate of treatment failure/relapse was significantly lower in Cef1 group compared with that in ASP group (OR, 0.664; 95% CI, 0.509-0.866; p = 0.002).The incidence rate of nephrotoxicity was significantly lower in Cef1 group compared with that in ASP group (OR, 0.296; 95% CI, 0.167-0.525; p < 0.001).

Abbreviation: ASP: Anti-staphylococcal penicillin; Cef1:first-generation cephalosporin

Pooled ORs for primary outcomes (90-day all-cause mortality)

A total of 9 studies (4807 patients) described 90-day all-cause mortality. The 90-day all-cause mortality rate was significantly lower in the Cfz group than in the ASP group (OR, 0.675; 95% confidence interval [CI], 0.485–0.938; p=0.019, low quality of evidence; Figure 2, Supplementary Figure S1).

Pooled ORs for secondary outcomes (30-day all-cause mortality, treatment failure/relapse and nephrotoxicity)

A total of 12 studies (12176 patients) described the incidence of 30-day all-cause mortality. The 30-day all-cause mortality rate was significantly lower in the Cfz group than in the ASP group (OR, 0.681; 95% CI, 0.533–0.869; p=0.002, low quality of evidence; Figure 2, Supplementary Figure S2).

A total of 11 studies (4829 patients) described the incidence of treatment failure/relapse. The incidence rate of treatment failure/relapse was significantly lower in the Cfz group than in the ASP group (OR, 0.664; 95% CI, 0.509–0.866; p=0.002, low quality of evidence; Figure 2, Supplementary Figure S3).

A total of 6 studies (1188 patients) described the incidence of nephrotoxicity. The incidence rate of nephrotoxicity was significantly lower in the Cfz group than in the ASP group (OR, 0.296; 95% CI, 0.167–0.525; p<0.001, low quality of evidence; Figure 2, Supplementary Figure S4).

Pooled ORs for primary and secondary outcomes in the trial sequential analysis

In the trial sequential analysis between the Cfz and APS groups, the overall OR for 90-day all-cause mortality was 0.770 (95% CI, 0.2541–1.113; p=0.091; Figure 3, Supplementary Figure S5a); for 30 days all-cause mortality, it was 0.780 (95% CI, 0.569–10.740; p=0.0729. Figure 3, Supplementary Figure S5b); for treatment failure/relapse, it was 0.695 (95% CI, 0.485–0.990; p=0.008; Figure 3, Supplementary Figure S5c); and for nephrotoxicity, it was 0.600 (95% CI, 0.006–6.647; p=0.078; Figure 3, Supplementary Figure S5d).

Funnel plot for the overall OR of the included studies for primary and secondary outcomes

We constructed a funnel plot to examine underlying heterogeneity. With regard to OR heterogeneity, the overall I^2 value for the included studies was calculated. In the funnel plot of the OR for event evaluation, the I^2 value for 90-day all-cause mortality was 47.6% (p=0.054; Supplementary Figure S6a); for 30-day all-cause mortality, it was 27.7% (p=0.173; Supplementary Figure S6b); for treatment failure/relapse, it was 0% (p=0.716;

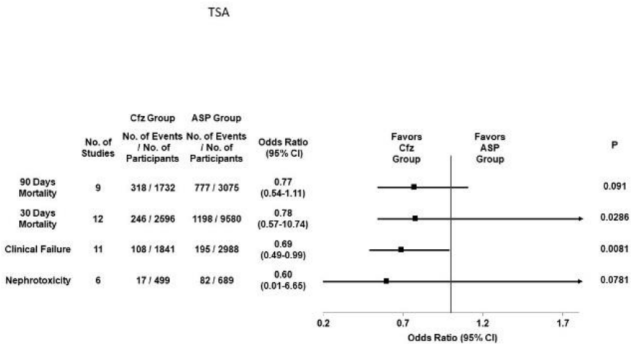

Figure 3: Trial sequential analysis of the odds ratio for all outcomes between two groups.

Trial sequential analysis of the odds ratio for all outcomes between two groups.
In the trial sequential analysis between the Cef1 and APS groups, the overall or of 90 days all-cause mortality was 0.770 (95% CI, 0.2541-1.113; p =0.091), that of 30 days all-cause mortality was 0.780 (95% CI, 0.569-10.740; p = 0.0729), treatment failure/relapse was 0.695 (95% CI, 0.485-0.990; p =0.008) and that of nephrotoxicity was 0.600 (95% CI, 0.006-6.647; p = 0.078).

Abbreviation: ASP: Anti-staphylococcal penicillin; Cef1:first-generation cephalosporin

Supplementary Figure S6c); and for nephrotoxicity, it was 32.9% (p=0.136; Supplementary Figure S6d).

DISCUSSION

Our meta-analysis and trial sequential analysis showed that according to the current evidence, both Cfz and ASP could effectively reduce the all-cause mortality rate and incidence rate of adverse reactions in patients with MsSaB. Although the all-cause mortality rate and adverse reaction rate was significantly lower in the treated group than in the control group, this study had heterogeneity and underlying variance in the outcomes because our study included only non-randomized cohort studies. In addition, the trial sequential analysis showed that the information sizes were inadequate. This comprehensive meta-analyses and trial sequential analysis of the available data demonstrated that treatment with Cfz was not associated with an increased all-cause mortality rate and incidence rate of adverse reaction. Our updated analysis suggested that caution is warranted. Routine prescription of Cfz might as good as prescription of ASP for treating patients with MsSaB.

Our meta-analysis and trial sequential analysis showed that prescribing Cfz to patients with MsSaB could effectively reduce the all-cause mortality rate and incidence rate of treatment failure/relapse as compared to ASP. This is consistent with previous studies.[41-43] Lee *et al.* reported that treatment failure rates were not significantly different between two groups in MsSaB patients,[41] as well as Li *et al.*'s report.[31] Bai *et al.* reported no significant clinical difference in mortality between two groups for the treatment of MsSaB, but showed that cefazolin was associated with a trend for relapses of MsSaB without significant difference.[43] The production of β-lactamases was not evaluated in the current study and some recent studies reported the presence of the CIE when patients were treated with cefazolin.[27,28] In Chong *et al.* s study, patients treated with cefazolin for MsSaB exhibited a pronounced CIE that was not associated with clinical outcomes and treatment failure rate.[27] In addition, our study did not assess the treatment failure/relapse caused by persistent MsSaB in high burden infections. Moreover, some recent studies found a non-significant difference between the two groups for high burden infections such as endocarditis.[28,45] In this study, the Cfz group was not associated with a higher mortality rate than the ASP group in the treatment for MsSaB patients, particularly those without CIE and high burden infections.

Additionally, our study showed that the rates of adverse reactions were significantly lower in the Cfz group than in the ASP group for treating patients with MsSaB. The findings are similar to the previous reports.[21,26,31,44] In the ASP group, the common adverse reaction was nephrotoxicity and Hoppes *et al.* described different nephrotoxicity caused by nafcillin usage for one year.[47] Additionally, Youngster *et al.* observed more renal dysfunction in the nafcillin group than in the cefazolin group (11.4% versus 3.3%; p=0.006).[26] A therapy guidelines described that patients to be discharged home on cefazolin but not on nafcillin due to the tolerance and compliance issues.[48] While the direct and indirect causes of ASP nephrotoxicity is still uncertain, the safety profile of Cfz may be advantageous when treating MsSaB. Concerning allergy to penicillin, approximately 10% of patients report an allergy to penicillin. The incidence of anaphylaxis due to penicillin is 0.02–0.04% and is mediated by a type 1 hypersensitivity reaction. Overall, cross-reactivity with penicillin groups is less than 3% for cephalosporin groups.[20] In patients with penicillin allergy and renal function impairment, prescription of Cfz might be safer than prescription of ASP when treating MsSaB, according to current updated comprehensive meta-analyses and trial sequential analysis.

This study is clinically important with wide applications. First, Cfz could be considered as a first-line agent because of non-inferior evidence to ASP for the treatment of MsSaB; this suggestion is consistent with other recent studies.[4,31,41-43] Second, Cfz is often a more tolerable option and has fewer adverse reactions than ASP.

There are some limitations to this study. First, the studies included in the primary analysis had different outcome measurements from different participants in various clinical settings. Only one among the 16 studies had a concurrent randomized control group. Confounding factors which possibly impacted outcomes had not been evaluated due to differences in the study individuals, disease severity and setting between individual studies made the study population highly heterogeneous for the outcome measurements. Second, the number of high bacterial burden infections and the prevalence of the CIE are ultimately unknown in our study. Third, we defined the threshold and criteria for tendency according to Hemmingsen *et al.* in the trial sequential analysis,[38] and it could be lead to potential detection bias. We have minimized publication bias by improving the methods of study identification, data selection and statistical analysis. These processes would strengthen the stability and accuracy of the meta-analysis. Moreover, the findings of this meta-analysis are reliable in providing suggestions for clinical care improvement.

CONCLUSION

Based on the evidence from 16 studies with over 13847 patients from four continents, this study showed that prescription of Cfz might as good as prescription of ASP for treating patients with MsSaB and both could effectively reduce the all-cause mortality rate and rate of adverse reaction. Because of heterogeneity, underlying variance and inadequate information sizes, our updated analysis suggests that caution is warranted. Further well-conducted randomized controlled trials are urgently needed to conclusively evaluate best drug of choice in patients with MsSaB and improve the all-cause mortality rate and adverse reaction.

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Ethical approval

The study was approved by the institutional review board of Changhua Christian Hospital (CCH IRB No. 180801).

CONFLICT OF INTEREST

All authors declare that they have no competing interests. The sponsors had no role in the design, execution, interpretation, or writing of the study.

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Authorship statement

Conception and design of study: CHC, YMC, HMC, YJC, LJL, HCY

Acquisition of data: CHC and YJC

Analysis and/or interpretation of data: CHC, YMC, YJC

Drafting the manuscript: CHC and YMC

Revising the manuscript critically for important intellectual content: CHC and CYM

Approval of the version of the manuscript to be published: CHC, YMC, HMC, YJC, LJL, HCY

ABBREVIATIONS

ASP: Anti-staphylococcal penicillins; **Cfz:** Cefazolin; **MsSaB:** Methicillin-sensitive *S. aureus* bacteremia; **OR:** Odds ratio; **C:** Confidence Interval; **LOS:** loss of consciousness; **MRSA:** Methicillin-sensitive *S. aureus*; **CIE:** Cefazolin inoculum effect; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation.

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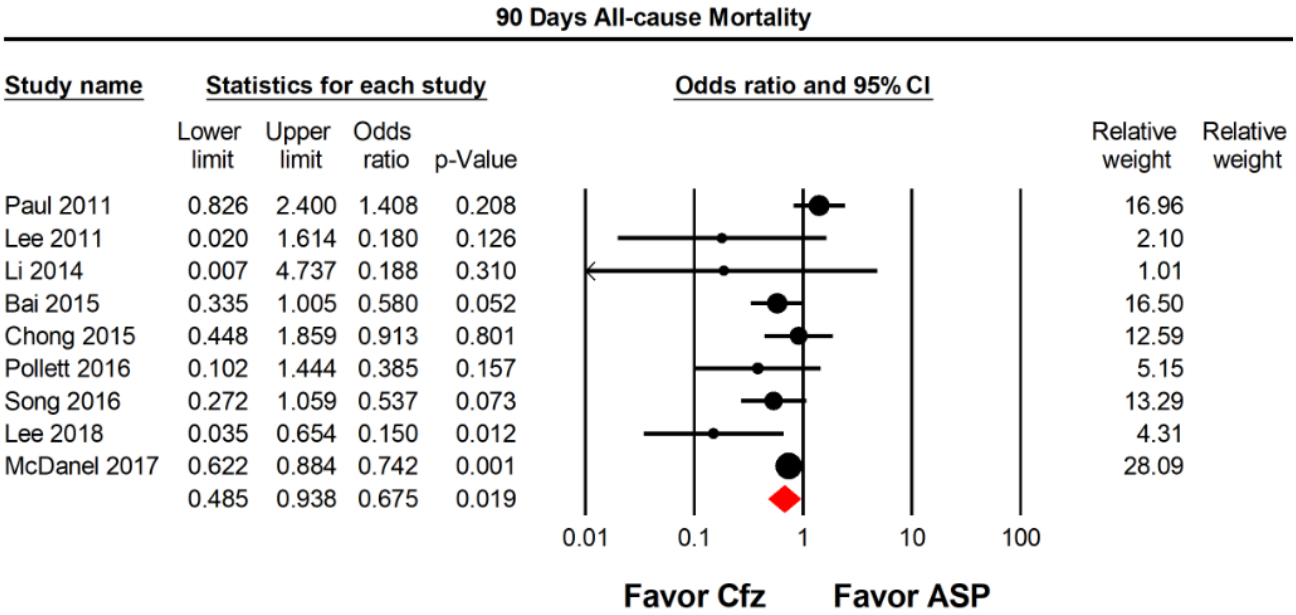
SUPPLEMENTARY FIGURES

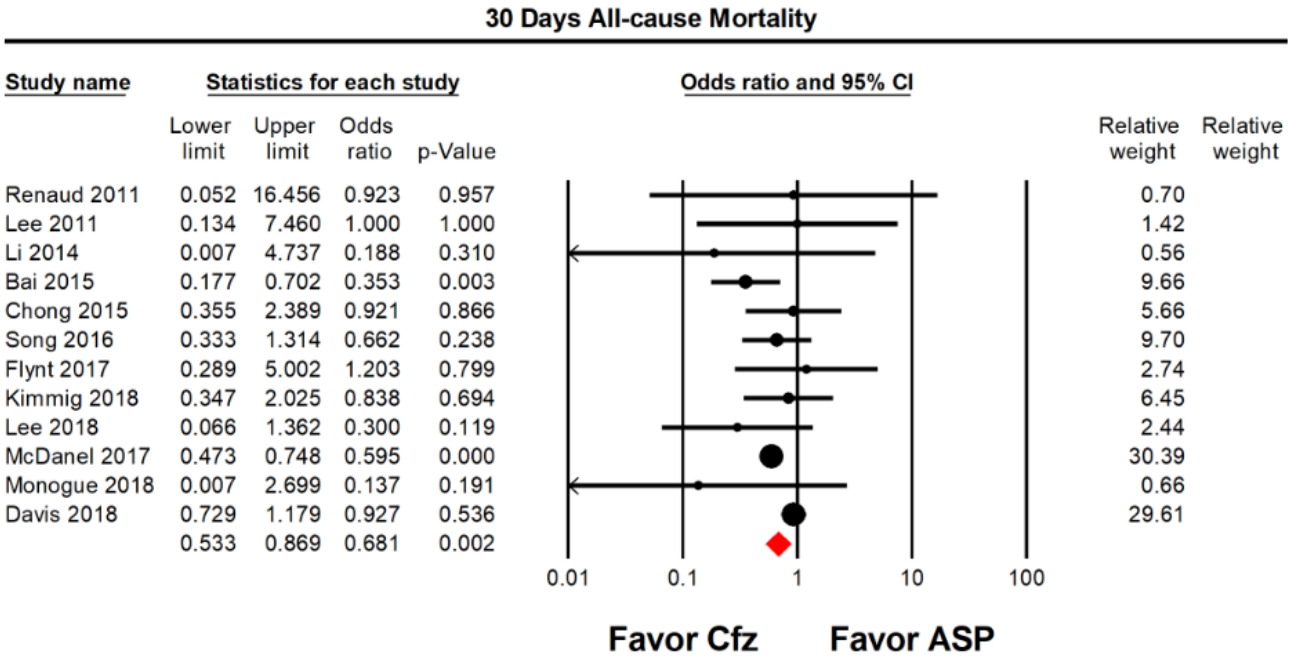


Supplementary Figure 1: Forest plot of the overall odds ratios for 90 days all-cause mortality between two groups.

The random effects model of overall odds ratio showed a significant overall effect of interventions in reducing the risk of 90 days all-cause mortality compared with that of the control condition (OR, 0.675; 95% CI, 0.485-0.938; p = 0.019, low quality of evidence).

Abbreviation : ASP: Anti-staphylococcal penicillin

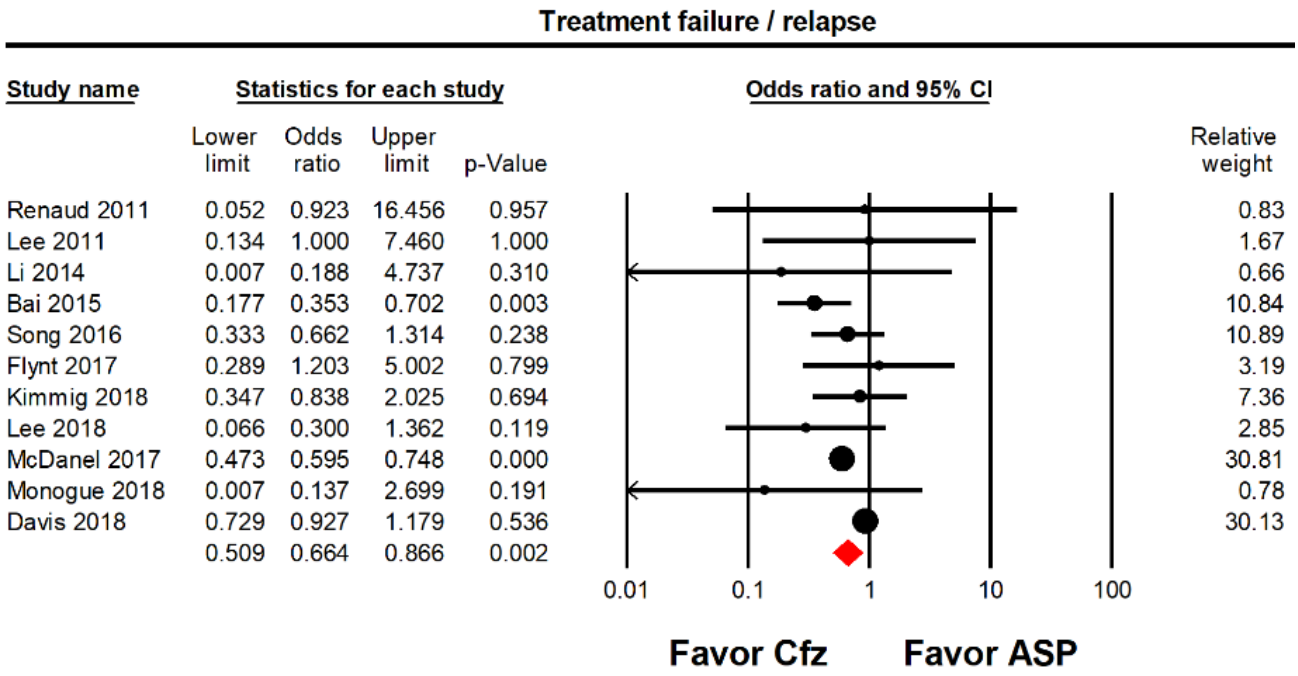
Notes: The outcome measures were determined by the odds ratios (ORs), and a random effects model with pool individual ORs was used. Analyses were conducted using the Comprehensive Meta-Analysis software version 3.0 (Biostat, NJ, USA). Between-trial heterogeneity was determined using I^2 tests. Statistical 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%. And, values > 50% were regarded as considerable heterogeneity[36]. Funnel plots and Egger's test were used to examine potential publication bias[36]. Statistical significance was defined as a *P*-value < 0.05. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[37].



Supplementary Figure 2: Forest plot of the overall odds ratios for 30 days all-cause mortality between two groups.

The random effects model of overall odds ratio showed a significant overall effect of interventions in reducing the risk of developing 30 days all-cause mortality compared with that of the control condition (OR, 0.681; 95% CI, 0.533-0.869; p = 0.002, low quality of evidence).

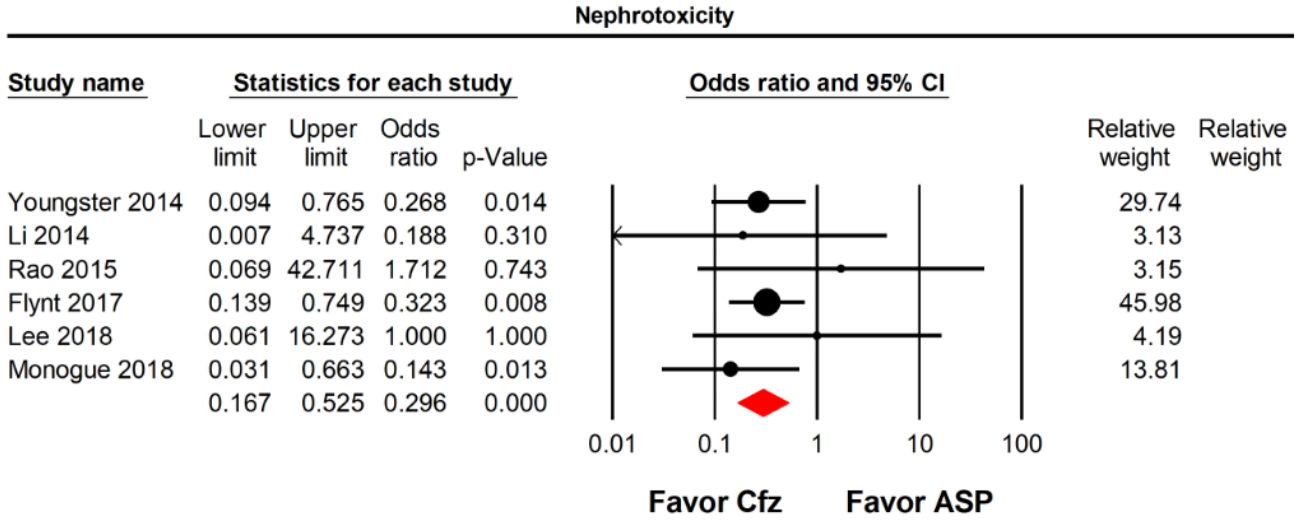
Abbreviation : ASP: Anti-staphylococcal penicillin



Supplementary Figure 3: Forest plot of the overall odds ratios for treatment failure/relapse between two groups.

The random effects model of overall odds ratio showed a significant overall effect of interventions in reducing the risk of developing treatment failure/relapse compared with that of the control condition (OR, 0.644; 95% CI, 0.509-0.866; p = 0.002, low quality of evidence).

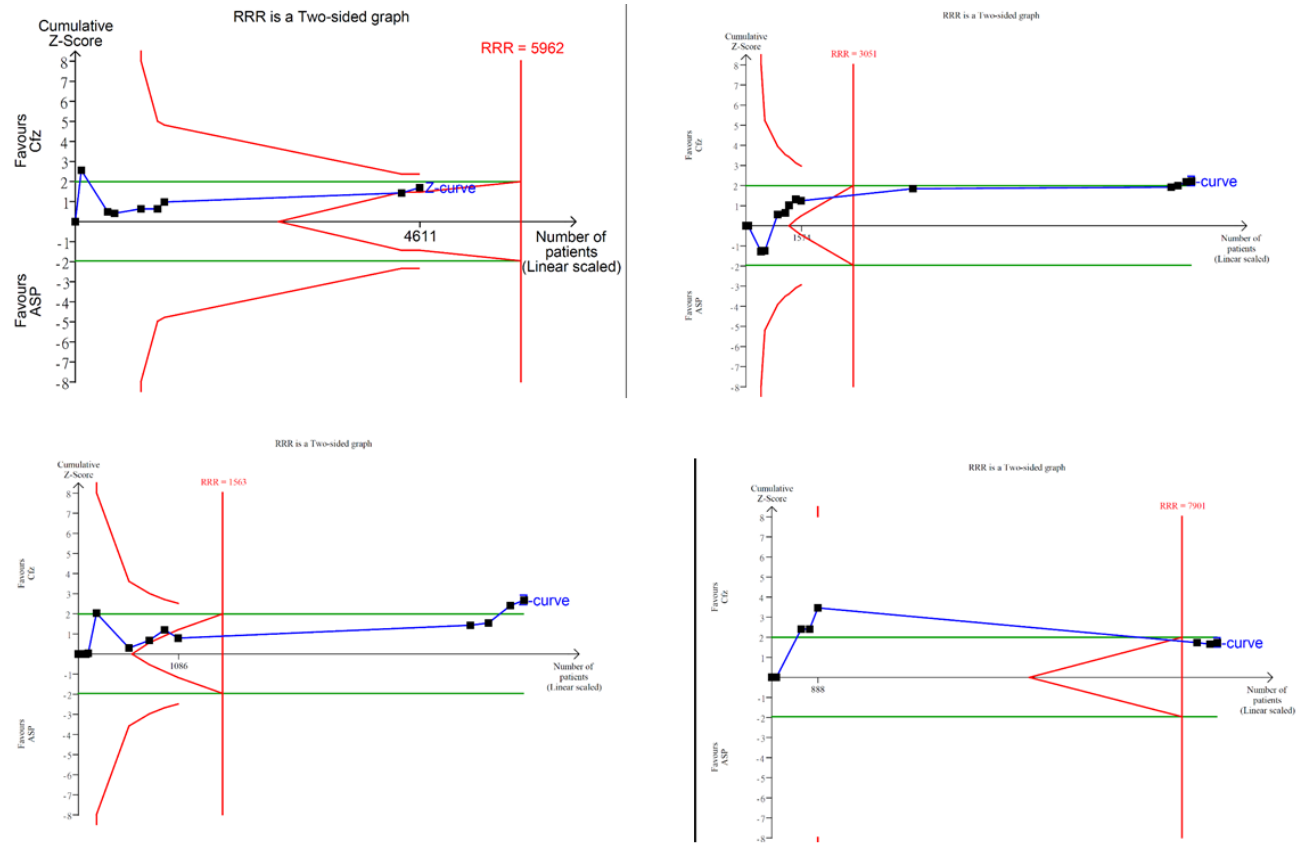
Abbreviation : ASP: Anti-staphylococcal penicillin



Supplementary Figure 4 :Forest plot of the overall odds ratios for nephrotoxicity between two groups.

The random effects model of overall odds ratio showed a significant overall effect of interventions in reducing the risk of developing nephrotoxicity compared with that of the control condition (OR, 0.296; 95% CI, 0.167-0.525; $p < 0.001$, low quality of evidence).

Abbreviation : ASP: Anti-staphylococcal penicillin



Supplementary Figure 5: Trial sequential analysis of the odds ratio for all outcomes between two groups.

(a) Trial sequential analysis of a 90 days all-cause mortality. Trial sequential analysis of 9 studies with a lower risk of bias in reporting all-cause mortality, with a control event proportion of 10%, diversity of 94%, type I error of 5%, power of 80%, and relative risk reduction of 30%. The required information size of 5962 was not achieved, and none of the boundaries for benefit, harm, or futility were crossed, leaving the meta-analysis inconclusive at a 30% relative risk reduction. The overall OR of 90 days all-cause mortality was 0.770 (95% CI, 0.541-1.113; p =0.091)

(b) Trial sequential analysis of 30 days all-cause mortality. Trial sequential analysis of 12 studies with low risk of bias reporting exit-site infection, with a control event proportion of 12%, diversity of 0%, type I error of 5%, power of 80%, and relative risk reduction of 30%. The required information size of 3051 was not achieved, and none of the boundaries for benefit, harm, or futility were crossed, leaving the meta-analysis inconclusive at a 30% relative risk reduction. The OR of 30 days all-cause mortality was 0.780 (95% CI, 0.569-10.740; p = 0.029).

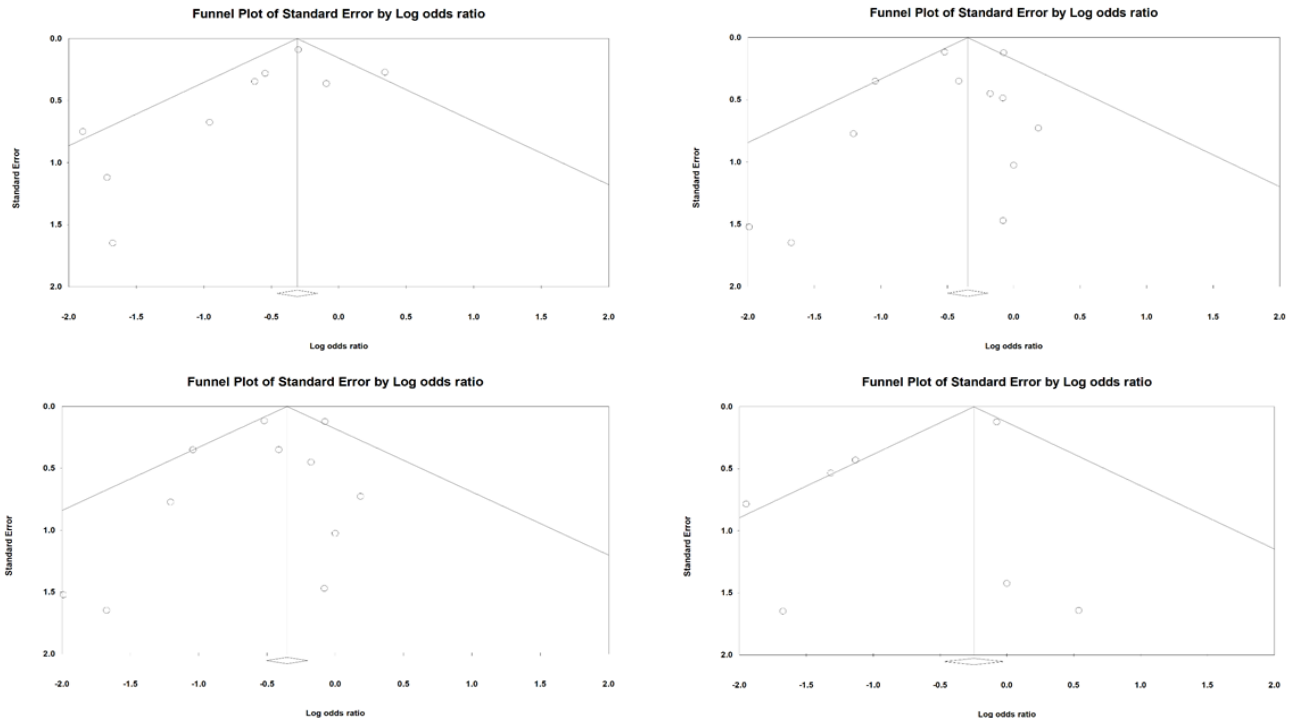
(c) Trial sequential analysis of treatment failure/relapse. Trial sequential analysis of 11 studies with low risk of bias reporting exit-site infection, with a control event proportion of 12%, diversity of 0%, type I error of 5%, power of 80%, and relative risk reduction of 30%. The required information size of 1563 was not achieved, and none of the boundaries for benefit, harm, or futility were crossed, leaving the meta-analysis inconclusive at a 30% relative risk reduction. The OR of treatment failure/relapse was 0.695 (95% CI, 0.485-0.990; p =0.008)

(d) Trial sequential analysis of nephrotoxicity. Trial sequential analysis of 6 studies with low risk of bias reporting exit-site infection, with a control event proportion of 12%, diversity of 0%, type I error of 5%, power of 80%, and relative risk reduction of 30%. The required information size of 7901 was not achieved, and none of the boundaries for benefit, harm, or futility were crossed, leaving the meta-analysis inconclusive at a 30% relative risk reduction. The OR of nephrotoxicity was 0.600 (95% CI, 0.006-6.647; p = 0.078)

Abbreviation : ASP: Anti-staphylococcal penicillin

Note 1: In trial sequential analyses, the inconsistence of heterogeneity (I^2) adjusted by required information size was calculated. According to Hemmingsen[38], the required information size was calculated with an intervention effect of a 30% relative risk reduction, an overall 5% risk of a type I error, and a risk of a type II error of 20%. All trial sequential analyses were performed using TSA version 0.9 beta (www.ctu.dk/tsa) for these analyses.

Notes 2: The solid blue line is the cumulative Z-curve. The vertical black dashed line is the required information size. The green dashed lines represent the trial sequential monitoring and futility boundaries.

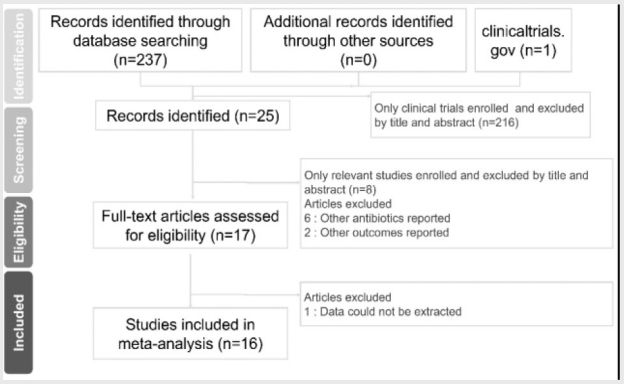


Supplementary Figure 6: Funnel plot of the odds ratio for all outcomes between two groups.

(a) Funnel plot of the odds ratio of 90 days all-cause mortality. I^2 value, 47.6%; $p = 0.054$. Egger's test revealed the existence of significant publication bias regarding the overall odds ratios. A P-value is indicated for A P-value is indicated for each case.
(b) Funnel plot of the odds ratio of 30 days all-cause mortality. I^2 value, 27.7%; $p = 0.173$. Egger's test revealed the existence of significant publication bias regarding the overall odds ratios. A P-value is indicated for A P-value is indicated for each case.
(c) Funnel plot of the odds ratio of treatment failure/relapse. I^2 value, 0%; $p = 0.716$. Egger's test revealed the existence of significant publication bias regarding the overall odds ratios. A P-value is indicated for A P-value is indicated for each case.
(d) Funnel plot of the odds ratio of nephrotoxicity. I^2 value, 32.9%; $p = 0.136$. Egger's test revealed the existence of significant publication bias regarding the overall odds ratios. A P-value is indicated for A P-value is indicated for each case.

Note: 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%. And, values > 50% were regarded as considerable heterogeneity[36]. Funnel plots and Egger's test were used to examine potential publication bias[36]. Statistical significance was defined as a *P*-value < 0.05.

PICTORIAL ABSTRACT



SUMMARY

Out of 237 potentially eligible studies, we excluded irrelevant studies and finally, 16 studies with a total of 13847 patients were included in this meta-analysis.

About Authors

Chang-Hua Chen graduated from China Medical College in 1981, and he served at Changhua Christian Hospital until now. In addition , he got Ph.D. degree from National Chung Hsing University in 2008. And he became Associate Professor at Ph.D. Program in Translational Medicine and Rong Hsing Research Center For Translational Medicine of National Chung Hsing University, Taiwan.

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