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Efficacy and safety of ceftaroline: systematic review and meta-analysis

Maria T. Rosanova, Pedro S. Aguilar, Norma Sberna and Roberto Lede

Abstract

Background: Resistance to antibiotics is steadily increasing. Ceftaroline has a broad spectrum of activity against clinically relevant gram-positive strains including methicillin-resistant *Staphylococcus aureus*.

Objectives: This systematic review was conducted to evaluate whether ceftaroline is effective and safe, leading to a lower rate of treatment failures than comparators.

Material and methods: Studies were included if they were comparing the efficacy and safety of ceftaroline with other antibiotics.

Data sources: Using the search terms 'ceftaroline' or 'ceftaroline fosamil', a search strategy was developed. The efficacy endpoint was the rate of treatment failure, while the safety endpoint was the incidence of adverse events. Heterogeneity bias was estimated using the *Q*-test, and publication bias was estimated using Egger's test. Null hypothesis was rejected if *p* value was less than 0.05.

Results: Only 10 studies were included.

Synthesis of results: The risk of treatment failure was significantly lower for ceftaroline than for comparators, and cumulative meta-analysis showed that the effect size was relevant and precise. Pooled risk ratio was 0.79 (95% confidence interval = 0.65–0.95). The rates of adverse events were similar among the studies, and there were no statistically significant differences between groups. For this endpoint, there was a significant heterogeneity among studies ($p = 0.03$). Pooled risk ratio for adverse events was 0.98 (95% confidence interval = 0.87–1.10), without a statistical difference.

Discussion: The risk of treatment failure was significantly lower for ceftaroline than comparators, while the rate of adverse events was similar. To the best of our knowledge, this is the first systematic review on the efficacy and safety of ceftaroline including children and adults. A limitation is that no randomized controlled trials were found in non-complicated skin- and soft-tissue infection and non-community-acquired pneumonia infections; only few cases with methicillin-resistant *Staphylococcus aureus* isolations and no patients admitted to the intensive care unit were evaluated.

Interpretation: Ceftaroline may be an option of treatment in complicated skin- and soft-tissue infection and community-acquired pneumonia.

Keywords: Ceftaroline, systematic review, soft tissue infection, efficacy, safety

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Introduction

Resistance to antibiotics has been steadily increasing, posing a growing worldwide health problem.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a common cause of complicated skin infections and pneumonia, among others, leading to the need for new effective and safe therapies.

Vancomycin remains the first option in the management of patients with invasive MRSA infections;

however, renal toxicity, the narrow spectrum, low concentration in tissues, and an increase in resistance have warranted new treatment alternatives.

Ceftaroline fosamil is a cephalosporin antimicrobial that has generated much interest as a potential treatment option. However, detailed descriptions of its use remain limited.[1] As it is the case of other cephalosporins, the antibacterial activity of ceftaroline is the result of binding to essential penicillin-binding proteins (PBPs) inhibiting bacterial cell wall synthesis.[1,2]

Ceftaroline has a broad spectrum of activity against clinically relevant gram-positive, strains including MRSA and resistant *Streptococcus pneumoniae* strains, as well as some gram-negative pathogens involved in complicated skin- and soft-tissue infections (cSSTI) and community-acquired pneumonia (CAP).[3,4] Currently, the drug has been approved by the US Food and Drug Administration (FDA) to be used in adults and children (from 2 months of age) with cSSTI caused by methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.[1–3] In addition, the drug has been approved by the FDA for CAP caused by *Streptococcus pneumoniae*, methicillin-sensitive, *Staphylococcus aureus* (non-MRSA), *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumonia*, and *Klebsiella oxytoca*.[1,3–5] Nevertheless, data on the clinical use of ceftaroline are scarce, especially in the pediatric population.[5]

Objective: This systematic review was conducted to evaluate efficacy and safety of ceftaroline and to assess if the drug is associated with a lower rate of treatment failures compared to antibiotic comparators. The secondary aim was to assess effectiveness of the drug in infections in which MRSA was isolated.

Materials and methods

Search strategies: A literature search was conducted to identify all clinical trials comparing safety and efficacy of ceftaroline *versus* any or none comparator using the strategy described in Table 1. Only articles published in English, Spanish, or French published up to 4 December 2017 were reviewed. Efficacy endpoint was the treatment failure rate because that is the main concern at the moment of antibiotic prescription. The safety endpoint was the incidence of adverse events.

Study selection: Data extraction and qualitative assessment were performed by two reviewers (M.T.R. and N.S.) who independently appraised the literature and considered only randomized controlled trials (RCTs) for further assessment. In case of disagreement, a third reviewer (R.L.) analyzed the data and managed the scientific discussion until consensus was reached.

A study qualified if (a) it was a RCT and (b) it compared the efficacy and safety of ceftaroline with other antibacterial agents or placebo. Both blinded and open-label trials were included. The methodological quality of the included studies was assessed using the Jadad scale.[6] The Jadad scale is a five-point questionnaire (Table 2) in which each question is to be answered with either a yes or a no. Each yes scores a single point and each no, zero points. Trials scoring ≥ 2 were considered for evaluation.

Data analysis and statistical methods: Efficacy endpoint incidence was based on intention-to-treat (ITT) populations of each study, and relative risks were determined based on this measure. Pooled risk ratio (RR) and 95% confidence intervals (CIs) were calculated for failure and safety outcomes using the random-effects model (DerSimonian–Laird), in order to be more conservative. Calculations were carried out using the meta-analysis calculator by EpiData software version 3.1 (WHO). Heterogeneity bias was estimated using the Q-test. Potential publication bias was estimated using Egger's test. The null hypothesis was rejected if p value was less than 0.05. Systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Table 3).

Results

Included studies and their main characteristics: The literature search identified a total of 1021 potentially relevant abstracts. Screening by title and abstract, 30 RCTs were selected for initial evaluation. A total of 20 RCTs were excluded as they did not meet inclusion criteria or were duplications or new analysis of previously published studies. Finally, 10 full-text articles were selected to be potentially included in this review[7–16] (Figure 1).

Out of the 10 studies, three studies[13–15] were conducted in pediatric population (two for treatment of CAP[14,15] and one for cSSTI13); seven were

Table 1. Search strategy.

Database	Access platform	Date of access	No. of results
Medline	Elsevier	4 December 2017	49
Embase	Elsevier	4 December 2017	68
CINAHL	EBSCOhost	4 December 2017	48
Cochrane	Wiley Online Library	4 December 2017	59
SCI-EXPANDED	WOS	4 December 2017	499
Scopus	Elsevier	4 December 2017	918
Total			1641
Duplicates			620
Total without duplicates			1021
Medline (4 December 2017)			
#5		#4 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim)	49
#4		#3 AND [medline]/lim	812
#3		#1 OR #2	1299
#2		ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo:ab,ti	1299
#1		'ceftaroline'/mj OR 'ceftaroline fosamil'/mj	514
Embase (4 December 2017)			
#5		#4 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim)	68
#4		#3 AND [embase]/lim	1263
#3		#1 OR #2	1299
#2		ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo:ab,ti	1299
#1		'ceftaroline'/mj OR 'ceftaroline fosamil'/mj	514
CINAHL (4 December 2017) Filtro de RR.SS y ECAs de SIGN. CINAHL (ECAs) for EBSCO (created by Mark Clowes) http://www.sign.ac.uk/search-filters.html			
S19		S5 OR S18	48
S18		S1 AND S17	46
S17		S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	1,298,037
S16		TX allocat* random*	623
S15		(MH 'Quantitative Studies')	17,078
S14		(MH 'Placebos')	10,607

(Continued)

Table 1. (Continued)

Database	Access platform	Date of access	No. of results
S13		TX placebo*	97,797
S12		TX random* allocat*	11,005
S11		(MH 'Random Assignment')	45,352
S10		TX randomi* control* trial*	189,585
S9		TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	952,488
S8		TX clinic* n1 trial*	304,883
S7		PT Clinical trial	85,443
S6		(MH 'Clinical Trials +')	230,020
S5		S1 AND S4	10
S4		S2 OR S3	135,754
S3		(MH 'Meta Analysis') or (TI (meta-analy* or metaanaly*)) or (AB (meta-analy* or metaanaly*))	53,544
S2		(TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (TI (integrative n3 review)) or (AB (integrative n3 review)) or (JN 'Cochrane Database of Systematic Reviews') or (TI ...	135,754
S1		TI (ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo) OR AB (ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo)	83
Cochrane Library (4 December 2017)			
#1		ceftaroline or 'ceftaroline fosamil' or teflaro or zinforo:ti,ab,kw (Word variations have been searched)	59
Science Citation Index Expanded (SCI-EXPANDED; 4 December 2017)			
#1		(TI = (ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo) OR TS = (ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo)) AND Idioma: (English OR Spanish) AND Tipos de documento: (Article OR Review) Índices = SCI-EXPANDED Período de tiempo = Todos los años	499
Scopus (4 December 2017)			
5		TITLE-ABS-KEY (ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo) AND (EXCLUDE (DOCTYPE, 'le') OR EXCLUDE (DOCTYPE, 'no') OR EXCLUDE (DOCTYPE, 'sh') OR EXCLUDE (DOCTYPE, 'ed') OR EXCLUDE (DOCTYPE, 'cp') OR EXCLUDE (DOCTYPE, 'ch')) AND (EXCLUDE (SUBJAREA, 'CHEM') OR EXCLUDE (SUBJAREA, 'AGRI') OR EXCLUDE (SUBJAREA, 'CENG') OR EXCLUDE (SUBJAREA, 'SOCI')) AND (EXCLUDE (SRCTYPE, 'k'))	918

Table 2. Jadad score template.

Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1

Table 3. PRISMA 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; conclusion and implications of key findings; and systematic review registration number.	Abstract form #1–2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Text #1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Text #1–2
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.	The protocol was not published
Eligibility criteria	6	Specify study characteristics (e.g. PICOS and length of follow up) and report characteristics (e.g. years considered, language, and publication status) used as criteria for eligibility, giving rationale.	#2
Information sources	7	Describe all information sources (e.g. databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched.	Table 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1 and Methods section
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).	#3
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.	Figure 1 # 3

(Continued)

Table 3. (Continued)

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g. PICOS and funding sources) and any assumptions and simplifications made.	#3
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.	#2–3–4
Summary measures	13	State the principal summary measures (e.g. risk ratio and difference in means).	#3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^1) for each meta-analysis.	#3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias and selective reporting within studies).	#3–5
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses and meta-regression), if done, indicating which were pre-specified.	No
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.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, and follow-up period) and provide the citations.	Table 4
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).	Tables 5–6
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.	Tables 5–6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, and meta-regression (see item 16)).	Not done
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).	#6–7
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 and reporting bias).	#8
Conclusion	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	#9
Funding			

Table 3. (Continued)

Section/topic	#	Checklist item	Reported on page #
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.	Not funding

Source: Moher D, Liberati A, Tetzlaff J, *et al.*; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; 6: e1000097. DOI: 10.1371/journal.pmed1000097.

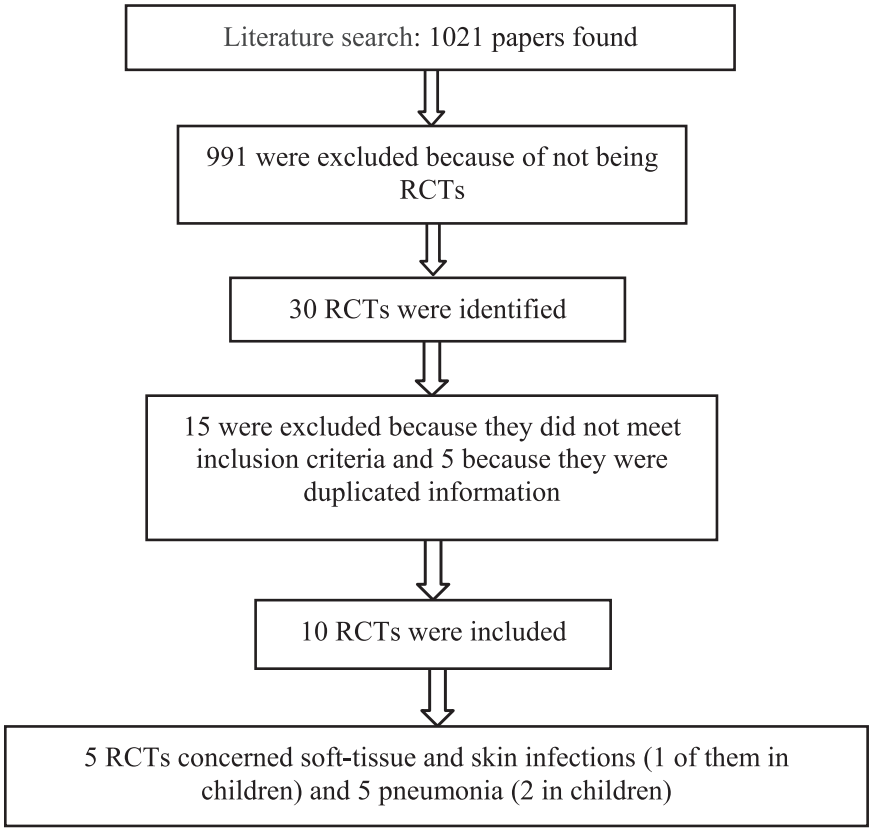

Figure 1. Flow diagram of the process of identification and selection of the articles included.

carried out in adult patients[7–12] (four for cSSTI and three for the treatment of CAP).

Table 4 summarizes the main characteristics of the articles included, and Table 5 shows the effect size, the proportional weight, and the pooled RR (95% CI) for the risk of failure of each study. Even when no heterogeneity was detected, pooled RR was calculated using the random-effects model (DerSimonian–Laird).

In individual studies, ceftaroline performance in CAP and cSSTI was not notably better than comparators regardless of the microbiological features (Table 6). However, cumulative meta-analysis revealed a lower risk of therapeutic failure for ceftaroline and the effect size became more relevant and precise when sample size increased, showing a sustained trend as in Figure 2.

Rates of adverse events were similar among the studies and there were no statistically significant differences between groups; however, significant heterogeneity among studies ($p=0.03$) was found for this endpoint. Pooled RR for adverse events was 0.98 (95% CI=0.87–1.10). The most commonly reported adverse drug reactions for ceftaroline were rash, fever, and gastrointestinal symptoms.[7–16]

In the majority of studies, the rate of direct Coombs test seroconversion was higher in the ceftaroline group than in the comparator groups.

Table 4. Main characteristics of the included studies.

Authors	Study design	Intervention	Endpoints	Jadad score
Talbot and colleagues[7]	Randomized, observer-blinded trial	Patients were randomized (2:1) to receive intravenous ceftaroline ($n = 61$) or vancomycin with or without adjunctive i.v. aztreonam ($n = 27$) during 7–14 days.	Clinical cure rate	2
Wilcox and colleagues[8]	Randomized, multinational, double-blind, active-controlled, parallel group	Adult patients with cSSTI requiring intravenous therapy were randomized (1:1) to receive ceftaroline fosamil ($n = 348$) or vancomycin plus aztreonam ($n = 346$) during 5–14 days.	Clinical and microbiological response, adverse events, and laboratory tests	3
Corey and colleagues[9]	Randomized, multinational, double-blind, active-controlled, parallel group	Adult patients with cSSTI requiring intravenous therapy were randomized (1:1) to receive ceftaroline fosamil ($n = 353$) or vancomycin plus aztreonam ($n = 349$).	Clinical and microbiological response, adverse events, and laboratory tests	3
File and colleagues[10]	Double-blinded, randomized, multinational trial	Adults hospitalized in a non-intensive care unit setting with CAP were randomized (1:1) to receive ceftaroline fosamil i.v. ($n = 298$) or ceftriaxone i.v. ($n = 308$) every 24 h.	Non-inferiority clinical cure, microbiological response, and adverse events	4
Low and colleagues[11]	Double-blinded, randomized, multinational trial	Hospitalized adults with CAP of PORT risk class III or IV severity were randomized (1:1) to receive ceftaroline fosamil ($n = 315$) or ceftriaxone ($n = 307$) administered during 5–7 days in non-ICU	Non-inferiority clinical cure, microbiological response, and adverse events	4
Zhong and colleagues[12]	Randomized, controlled, double-blind, non-inferiority with nested superiority trial	Adults with risk class III–IV acute community-acquired pneumonia were randomly assigned (1:1) to receive intravenous ceftaroline fosamil ($n = 381$) or ceftriaxone ($n = 383$) during 5–7 days.	Clinically cured, microbiological cure, and adverse events	4
Korczowski and colleagues[13]	Multicenter, randomized, observer-blinded, controlled trial	Patients with cSSTI were randomized (2:1) to receive intravenous ceftaroline fosamil ($n = 107$) or IV vancomycin or cefazolin, ±aztreonam ($n = 52$)	Clinically cured, microbiological cure, and adverse events	2
Blumer and colleagues[14]	Multicenter, randomized, observer-blinded, active-controlled trial	Patients were randomized 3:1 (stratified by age cohort) to receive ceftaroline fosamil ($n = 30$) or ceftriaxone plus vancomycin ($n = 10$)	Clinical cure rates, adverse events, and death	3
Cannavino and colleagues[15]	Multicenter, randomized, controlled trial	Patients were stratified into four age cohorts and randomized (3:1) to receive either intravenous ceftaroline fosamil ($n = 122$) or ceftriaxone ($n = 69$)	Treatment-emergent adverse events, clinical outcomes, and microbiologic responses	2
Dryden and colleagues[16]	Multicenter, randomized, double-blind, non-inferiority trial	Patients with cSSTI and systemic inflammation or comorbidities were randomized (2:1) to 600 mg every 8 h of intravenous ceftaroline fosamil ($n = 514$) or 15 mg/kg every 12 h of vancomycin plus aztreonam (1 g every 8 h) ($n = 258$) during 5–14 days.	Clinically cured, microbiological cure, and adverse events	4

CAP, community-acquired pneumonia; cSSTI, complicated skin- and soft-tissue infections; ICU, intensive care unit; PORT, pneumonia outcome research trial.

Table 5. Efficacy of the studies included: Therapeutic failure rate (intention-to-treat analyses).

Authors	Ceftaroline (*n*/*N*)	Comparator (*n*/*N*)	RR (95% CI)	Weight (%; random-effects model)
Talbot and colleagues[7] *n* = 99	8/67	6/32	0.63 (0.24–1.68)	3.2587
Wilcox and colleagues[8] *n* = 680	51/342	49/338	1.02 (0.71–1.47)	13.1184
Corey and colleagues[9] *n* = 698	47/351	50/347	0.92 (0.64–1.34)	12.8584
File and colleagues[10] *n* = 591	37/291	67/300	0.53 (0.37–0.75)	13.2904
Low and colleagues[11] *n* = 562	54/289	67/273	0.76 (0.55–1.04)	14.7704
Zhong and colleagues[12] *n* = 763	76/381	126/382	0.60 (0.47–0.77)	17.7685
Korczowski and colleagues[13] *n* = 159	16/107	8/52	0.97 (0.44–2.12)	4.7080
Blumer and colleagues[14] *n* = 38	5/29	2/9	0.77 (0.18–3.33)	1.5529
Cannavino and colleagues[15] *n* = 143	13/107	4/36	1.09 (0.38–3.14)	2.8151
Dryden and colleagues[16] *n* = 761	110/506	53/255	1.04 (0.0.78–1.39)	15.8592
Pooled RR (95% CI) random-effects model	*N* = 4494		0.79 (0.65–0.95)	100.00

CI, confidence interval; RR, risk ratio.

Nevertheless, no cases of hemolytic anemia were reported.

In order to analyze risk of treatment failure specifically in infections due to MRSA, a secondary analysis was performed including the six studies (357 patients) reporting these data.[7–9,12,13,16] Pooled RR was 0.71 (95% CI = 0.37–1.35).

No significant publication bias was detected ($p > 0.05$) at any stage (efficacy or safety analysis) of the meta-analysis, although its probability is close to the boundary of significance. Figure 3 shows the corresponding funnel plot for efficacy analysis (Q-test: 16.46; $p = 0.058$).

In other infections, such as endocarditis, osteoarticular infections, and bacteremia, only case series showing good results with ceftaroline fosamil were found;[17–21] however, these studies were not analyzed in this study.

Discussion

This systematic review was conducted to evaluate the risk of therapeutic failure and safety of ceftaroline in children and adults in order to assess the comparative effectiveness and safety of the drug as monotherapy against available comparators.

This meta-analysis suggests that ceftaroline was effective and well tolerated, consistent with the good safety profile of the cephalosporins.[22] This finding, which does not arise from the observation of the individual studies, is probably the result of the increasing sample size.

It is worth pointing out that the risk of therapeutic failure of ceftaroline was found to be significantly lower for both types of infection, and a sustained trend was seen in the cumulative meta-analysis.

Concerns arose, when all the included RCT studies were observed to be conducted only in patients with CAP or cSSTI infections, in patients who

Table 6. Safety of the studies included*.

Authors	Ceftarolina (*n*/*N*)	Comparator (*n*/*N*)	RR (95% CI)	Weight (%) (random-effects model)
Talbot and colleagues[7] *n* = 99	41/67	18/32	1.09 (0.76–1.56)	5.2523
Wilcox and colleagues[8] *n* = 680	64/341	82/339	0.96 (0.71–1.29)	9.84
Corey and colleagues[9] *n* = 698	165/351	167/347	0.95 (0.82–1.10)	19.2523
File and colleagues[10] *n* = 591	119/298	136/308	0.90 (0.75–1.09)	14.5085
Low and colleagues[11] *n* = 562	64/315	52/307	1.20 (0.86–1.67)	6.0972
Zhong and colleagues[12] *n* = 763	172/381	163/383	1.06 (0.90–1.25)	17.5802
Korczowski and colleagues[13] *n* = 159	23/106	12/53	0.96 (0.52–1.77)	1.9614
Blumer and colleagues[14] *n* = 38	12/30	8/10	0.50 (0.29–0.86)	2.5391
Cannavino and colleagues[15] *n* = 143	55/121	18/39	0.98 (0.67–1.46)	4.5392
Dryden and colleagues[16] *n* = 761	142/506	87/255	0.82 (0.66–1.03)	11.6117
Pooled RR (95% CI; random-effects model)	*N* = 4589		0.98 (0.87–1.10)	100.00

CI, confidence interval; RR, risk ratio.
*At least one adverse event.

were not admitted to intensive care units (ICUs) or were treated with different doses having different follow-up periods, or were using antibiotic comparators that are not typically indicated in the clinics for the treatment of these infections, among others' characteristics.

In CAP, ceftriaxone is the only cephalosporin that has been demonstrated superiority to penicillin in *Streptococcus pneumoniae*, even in penicillin-resistant strains, and the drug may be an option in these cases.[8] Ceftaroline may be useful against gram-positive organisms and in areas with a high incidence of MRSA infections.

For complicated pneumonia and patients in the ICU, antimicrobial therapy must be broadened to cover pathogens such as MRSA.

The study by Zhong and colleagues[12] was the only report that found non-inferiority, even superiority, of ceftaroline *versus* ceftriaxone for the management of CAP in Asian patients not admitted to the ICU. However, the conclusions of this study are of limited validity because of the observed risk of bias regarding the timing of assessment of clinical cure between groups, doses, and conflict of interest, among others' concerns.[23]

In other infections such as endocarditis, osteoarticular infections, and bacteremia, only case series showing good results with ceftaroline fosamil were found,[17–21] but these reports were not analyzed in this study.

The strengths of our study are that, to the best of our knowledge, this is the first systematic review

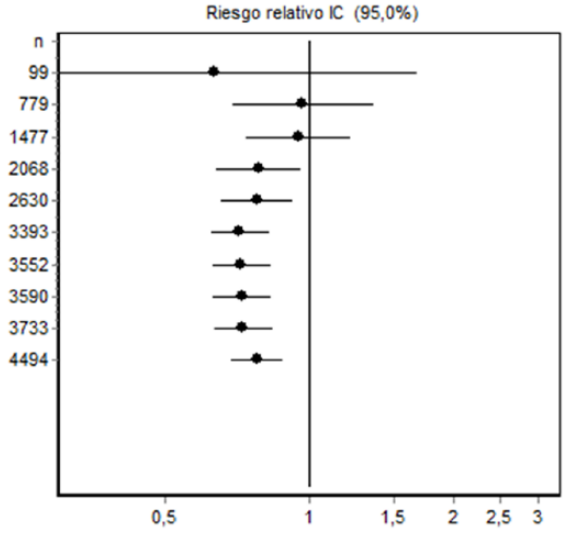

Figure 2. Risk of therapeutic failure: cumulative meta-analysis.
Cumulative meta-analysis shows that the risk of therapeutic failure with ceftaroline is lower than with comparators, and this is a sustained trend.

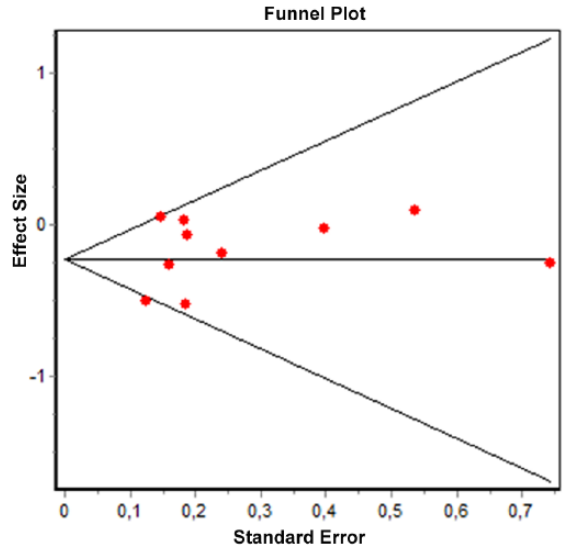

Figure 3. Risk of publication bias in efficacy analysis.
Figure 3 presents the corresponding funnel plot for efficacy analysis (Q-test: 16.46; $p = 0.058$).

and meta-analysis on the efficacy and safety of ceftaroline including children and adults, only RCTs were included, and that the quality of the studies included was assessed in detail.

Limitations are that no RCTs including other non-cSSTI and non-CAP infections were found, cases in which MRSA was isolated were few, and none of the patients was admitted to the ICU. Quality of evidence of studies carried out in other types of infection or in patients admitted to the ICU was limited. In addition, very few studies were conducted in children.

Inherent to systematic reviews, publication bias is always a potential problem, and although the comprehensive search strategy may overcome this issue and the funnel plot showed no relevant evidence of publication bias, this possibility can never be completely excluded.

Clinical implications: The superior efficacy of ceftaroline, its safety profile, and the possibility of its use as monotherapy decrease the need for combined antibiotic treatments, making the drug an attractive option in clinical practice.

Ceftaroline may be considered, particularly in patients with CAP and cSSTI that are intolerant or refractory to other antibiotics used as first-line treatment.

It is remarkable that none of the patients was studied in an ICU setting; however, given the effectiveness of ceftaroline, it may be speculated that even in patients admitted to the ICU, ceftaroline could be useful.

Future research: Further randomized and controlled studies are needed to better understand the role of ceftaroline in other non-CAP and non-cSSTI infections in ICU settings and in children.

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Conflict of interest statement
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References
1. Kiang TK, Wilby KJ and Ensom MH. A critical review on the clinical pharmacokinetics, pharmacodynamics, and clinical trials of ceftaroline. *Clin Pharmacokinet* 2015; 54: 915–931.

2. Scott LJ. Ceftaroline fosamil: a review in complicated skin and soft tissue infections and community-acquired pneumonia. *Drugs* 2016; 76: 1659–1674.

3. Jandourek A, Smith A, Llorens L, *et al*. Efficacy of ceftaroline fosamil for bacteremia associated with community-acquired bacterial pneumonia. *Hosp Pract* 2014; 42: 75–78.

4. Zasowski EJ, Trinh TD, Claeys KC, *et al.* Multicenter observational study of ceftaroline fosamil for methicillin-resistant Staphylococcus aureus bloodstream infections. *Antimicrob Agents Chemother* 2017; 61: e02015–e02016.

5. Juwon Y, Leah M, Molloy J, *et al.* Use of ceftaroline fosamil in children: review of current knowledge and its application. *Infect Dis Ther* 2017; 6: 57–67.

6. Jadad AR, Moore RA, Carrol D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.

7. Talbot GH, Thye D, Das A, *et al.* Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2007; 51: 3612–3615.

8. Wilcox MH, Corey GR, Talbot GH, *et al.* CANVAS 2: the second phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010; 65(Suppl. 4): iv53–iv65.

9. Corey GR, Wilcox MH, Talbot GH, *et al.* CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010; 65(Suppl. 4): iv41–iv51.

10. File TM Jr, Low DE, Eckburg PB, *et al.* Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis* 2010; 51: 1395–1405.

11. Low DE, File TM Jr, Eckburg PB, *et al.* FOCUS 2: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66(Suppl. 3): iii33–iii44.

12. Zhong NS, Sun T, Zhuo C, *et al.* Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. *Lancet Infect Dis* 2015; 15: 161–171.

13. Korczowski B, Antadze T, Giorgobiani M, *et al.* A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety and efficacy of ceftaroline versus comparator in pediatric patients with acute bacterial skin and skin structure infection. *Pediatr Infect Dis J* 2016; 35: e239–e247.

14. Blumer JL, Ghonghadze T, Cannavino C, *et al.* A multicenter, randomized, observer-blinded, active-controlled study evaluating the safety and effectiveness of ceftaroline compared with ceftriaxone plus vancomycin in pediatric patients with complicated community-acquired bacterial pneumonia. *Pediatr Infect Dis J* 2016; 35: 760–766.

15. Cannavino CR, Nemeth A, Korczowski B, *et al.* A randomized, prospective study of pediatric patients with community-acquired pneumonia treated with ceftaroline versus ceftriaxone. *Pediatr Infect Dis J* 2016; 35: 752–759.

16. Dryden M, Zhang Y, Wilson D, *et al.* A phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities. *J Antimicrob Chemother* 2016; 71: 3575–3584.

17. El Hajj M, Turgeon R and Wilby K. Ceftaroline fosamil for community-acquired pneumonia and skin and skin structure infections: a systematic review. *Int J Clin Pharm* 2017; 39: 26–32.

18. Cosimi R, Beik N, Kubiak D, *et al.* Ceftaroline for severe methicillin-resistant Staphylococcus aureus infections: a systematic review. *Open Forum Infect Dis* 2017; 2: 4–7.

19. Pasquale TR, Tan MJ, Trienski TL, *et al.* Methicillin-resistant Staphylococcus aureus nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. *J Chemother* 2015; 27: 29–34.

20. Casapao AM, Davis SL, Barr VO, *et al.* Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. *Antimicrob Agents Chemother* 2014; 58: 2541–2546.

21. Horcajada J and Canton R. Ceftarolina, un nuevo antimicrobiano de amplio espectro en la era de las Multirresistencias. *Enferm Infecc Microbiol Clin* 2014; 32(Suppl.2): 1–7.

22. Rank DR, Friedland HD and Laudano JB. Integrated safety summary of FOCUS 1 and FOCUS 2 trials: phase III randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66(Suppl. 3): iii53–iii59.

23. Pawluk SA and Wilby KJ. Ceftaroline fosamil for community-acquired pneumonia. *Lancet Infect Dis* 2015; 15: 999.