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

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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

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. 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 (cSSTIs) 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 cSSTIs 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 pneumoniae*, 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 \(\geq 2\) 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 cSSTI\(^13\)); 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)
- #4: #3 AND [medline]/lim
- #3: #1 OR #2
- #2: ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo:ab,ti
- #1: 'ceftaroline'/mj OR 'ceftaroline fosamil'/mj

#### Embase (4 December 2017)

- #5: #4 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim)
- #4: #3 AND [embase]/lim
- #3: #1 OR #2
- #2: ceftaroline OR 'ceftaroline fosamil' OR teflaro OR zinforo:ab,ti
- #1: 'ceftaroline'/mj OR 'ceftaroline fosamil'/mj

#### 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
- S18: S1 AND S17
- S17: S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
- S16: TX allocat* random*
- S15: (MH 'Quantitative Studies')
- S14: (MH 'Placebos')

(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} Indices = 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.

| Question                                                                 | Score |
|--------------------------------------------------------------------------|-------|
| 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**     |   | Identify the report as a systematic review, meta-analysis, or both.             | #1                |
| **Abstract**  |   | Provide a structured summary including, as applicable, background; objectives; | Abstract form     |
|               |   | data sources; study eligibility criteria, participants, and interventions;     | #1–2              |
|               |   | study appraisal and synthesis methods; results; limitations; conclusion        |                   |
|               |   | and implications of key findings; and systematic review registration number.   |                   |
| **Introduction** | | Describe the rationale for the review in the context of what is already known. | Text #1           |
| Rationale     | 3 | Provide an explicit statement of questions being addressed with reference to   | Text #1–2         |
|               |   | participants, interventions, comparisons, outcomes, and study design (PICOS).  |                   |
| **Methods**   |   | Indicate if a review protocol exists, if and where it can be accessed [e.g.   | The protocol was not published |
|               |   | Web address], and, if available, provide registration information including    |                   |
|               |   | registration number.                                                          |                   |
| Protocol and registration     | 5 | Specify study characteristics [e.g. PICOS and length of follow up] and report | #2                |
| Eligibility criteria          |   | characteristics [e.g. years considered, language, and publication status]     |                   |
|               |   | used as criteria for eligibility, giving rationale.                          |                   |
| Information sources           | 7 | Describe all information sources [e.g. databases with dates of coverage and   | Table 1           |
|               |   | contact with study authors to identify additional studies] in the search and  |                   |
|               |   | date last searched.                                                          |                   |
| Search                     | 8 | Present full electronic search strategy for at least one database, including    | Table 1 and Methods section |
|               |   | any limits used, such that it could be repeated.                            |                   |
| Study selection             | 9 | State the process for selecting studies (i.e. screening, eligibility, included in | #3                |
|               |   | systematic review, and, if applicable, included in the meta-analysis).       |                   |
| Data collection process      | 10| Describe method of data extraction from reports [e.g. piloted forms,         | Figure 1 #3       |
|               |   | independently, in duplicate] and any processes for obtaining and confirming   |                   |
|               |   | data from investigators.                                                     |                   |

(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. I²] 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 patients7−12 (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 colleagues⁷   | 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 colleagues⁸   | 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 colleagues⁹    | 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 colleagues¹⁰    | 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 colleagues¹¹     | 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 colleagues¹²   | Randomized, controlled, double-blind, non-inferiority 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 colleagues¹³ | 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 colleagues¹⁴  | 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 colleagues¹⁵ | 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 colleagues¹⁶  | 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 colleagues⁷  | 8/67              | 6/32             | 0.63 (0.24–1.68)     | 3.2587                          |
| Wilcox and colleagues⁸  | 51/342            | 49/338           | 1.02 (0.71–1.47)     | 13.1184                         |
| Corey and colleagues⁹   | 47/351            | 50/347           | 0.92 (0.64–1.34)     | 12.8584                         |
| File and colleagues¹⁰   | 37/291            | 67/300           | 0.53 (0.37–0.75)     | 13.2904                         |
| Low and colleagues¹¹    | 54/289            | 67/273           | 0.76 (0.55–1.04)     | 14.7704                         |
| Zhong and colleagues¹²  | 76/381            | 126/382          | 0.60 (0.47–0.77)     | 17.7685                         |
| Korczowski and colleagues¹³ | 16/107          | 8/52             | 0.97 (0.44–2.12)     | 4.7080                          |
| Blumer and colleagues¹⁴ | 5/29              | 2/9              | 0.77 (0.18–3.33)     | 1.5529                          |
| Cannavino and colleagues¹⁵ | 13/107          | 4/36             | 1.09 (0.38–3.14)     | 2.8151                          |
| Dryden and colleagues¹⁶  | 110/506           | 53/255           | 1.04 (0.0.78–1.39)   | 15.8592                         |
| Pooled RR (95% CI)      | 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. 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 colleagues⁷      | n = 99            | 41/67            | 18/32       | 1.09 (0.76–1.56)                 | 5.2523 |
| Wilcox and colleagues⁸      | n = 680           | 64/341           | 82/339      | 0.96 (0.71–1.29)                 | 9.84   |
| Corey and colleagues⁹       | n = 698           | 165/351          | 167/347     | 0.95 (0.82–1.10)                 | 19.2523|
| File and colleagues¹⁰       | n = 591           | 119/298          | 136/308     | 0.90 (0.75–1.09)                 | 14.5085|
| Low and colleagues¹¹        | n = 562           | 64/315           | 52/307      | 1.20 (0.86–1.67)                 | 6.0972 |
| Zhong and colleagues¹²      | n = 763           | 172/381          | 163/383     | 1.06 (0.90–1.25)                 | 17.5802|
| Korczowski and colleagues¹³ | n = 159           | 23/106           | 12/53       | 0.96 (0.52–1.77)                 | 1.9614 |
| Blumer and colleagues¹⁴     | n = 38            | 12/30            | 8/10        | 0.50 (0.29–0.86)                 | 2.5391 |
| Cannavino and colleagues¹⁵  | n = 143           | 55/121           | 18/39       | 0.98 (0.67–1.46)                 | 4.5392 |
| Dryden and colleagues¹⁶     | 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 Ceftarolone 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 colleagues¹² was the only report that found non-inferiority, even superiority, of ceftarolone 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 ceftarolone 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...
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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