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Clinical cure with ceftriaxone versus ceftaroline or ceftobiprole in the treatment of staphylococcal pneumonia: a systematic review and meta-analysis

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ABSTRACT

Ceftriaxone is an empirical antibiotic commonly used to treat pneumonia. However, its use to treat infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) is controversial given limited evidence of its clinical efficacy. The objective of this study was to compare the clinical efficacy of ceftriaxone with either ceftaroline or ceftobiprole in the treatment of pneumonia caused by MSSA. A systematic review and meta-analysis of randomised controlled trials (RCTs) comparing clinical cure in patients with pneumonia who received ceftriaxone versus those who received either ceftaroline or ceftobiprole was conducted. Patients who received ceftriaxone plus vancomycin were excluded. The PubMed, Embase and Cochrane Library databases as well as clinical trial registries were searched up to 8 June 2018. Risk differences (RDs) with 95% confidence intervals (CIs) were estimated using a random-effects model and assessing for heterogeneity (I^2). A total of five RCTs met the inclusion criteria; four used ceftaroline and one used ceftobiprole. Four studies included adults and one included paediatric patients. The adult studies included non-intensive care unit patients with mild-to-moderate community-acquired pneumonia. Clinical cure was statistically lower with ceftriaxone (RD, −28.5%, 95% CI −53.5% to −3.4%; $P = 0.026$; $I^2 = 16.321\%$) than with ceftaroline or ceftobiprole. In conclusion, ceftriaxone use was associated with higher clinical failure of MSSA pneumonia compared with ceftaroline or ceftobiprole. This supports the notion that ceftriaxone is not an ideal agent for the treatment of MSSA infections and adds new evidence against its use for MSSA pneumonia.

1. Introduction

The standard parenteral antibiotics used to treat methicillin-susceptible *Staphylococcus aureus* (MSSA) infections are antistaphylococcal penicillins and cefazolin [1,2]. These narrow-spectrum agents are highly effective against *S. aureus* but a major limitation in outpatient settings is that they require frequent daily administration. Ceftriaxone has a broader spectrum of activity, lower activity against *S. aureus* and may contribute to collateral resistance and *Clostridium difficile* infections; however, it can be administered once daily [3–6]. Given this convenient dosing, some institutions have started using ceftriaxone to treat outpatients with MSSA infections. Moreover, the Infectious Diseases Society of America (IDSA) guidelines for native vertebral osteomyelitis [2 g every 24 h (q24h)] and prosthetic joint infection (1–2 g q24h) list ceftriaxone as a treatment option for MSSA infections [7,8]. However, its use in this context is controversial given limited evidence of its impact on clinical outcomes. Indeed, all current studies on the effectiveness of ceftriaxone are of observational design and most include small sample sizes and likely placed patients with less severe disease in the ceftriaxone group [9].

More studies are required to assess the efficacy of ceftriaxone compared with standard antistaphylococcal agents in the treatment of MSSA infections. Unfortunately, randomised controlled trials (RCTs) are not expected to compare ceftriaxone with standard antistaphylococcal agents but rather with the newer

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cephalosporins ceftaroline and ceftobiprole, which are more active than ceftriaxone against MSSA but whose evidence of impact on clinical outcomes is limited [10–14]. Nevertheless, it may be possible to extrapolate the clinical impact of antistaphylococcal agents from that of the newer cephalosporins since both are more active against MSSA than ceftriaxone. This can provide additional data on the efficacy of ceftriaxone for MSSA infections and for the first time coming from RCTs by performing a meta-analysis pooling the small number of cases from each RCT. In addition to adding to this pool of evidence, this meta-analysis would be the first clinical study evaluating the efficacy of ceftriaxone for MSSA pneumonia. Continuing empirical antibiotic therapy without de-escalation is a common problem in clinical practice, therefore reduced ceftriaxone efficacy for MSSA pneumonia would promote de-escalation even further. Moreover, ceftriaxone can be convenient for certain scenarios such as outpatients with ceftriaxone-susceptible Gram-negative bacteria owing to its once-daily dosing if oral options are avoided. The purpose of this study was to compare the clinical efficacy of ceftriaxone with that of ceftaroline and ceftobiprole in the treatment of pneumonia caused by MSSA.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this systematic review and meta-analysis.

2.1. Search strategy and selection criteria

The Cochrane Library, Embase and PubMed bibliographic databases were searched using the keywords ‘ceftriaxone’, ‘ceftaroline’, ‘ceftobiprole’ and ‘pneumonia’. In addition, ClinicalTrials.gov, the EU Clinical Trials register and the WHO International Clinical Trials Registry Platform were searched for additional unpublished studies. All searches and data extractions were performed independently by two authors (AB and HW) up to 8 June 2018 without date or language restrictions. A third author (KE) evaluated any disagreement in the literature screening and reviewed the extracted data.

RCTs comparing clinical outcomes in patients with pneumonia caused by MSSA who received ceftriaxone versus those who received either ceftaroline or ceftobiprole were included. Patients who received ceftriaxone plus vancomycin were excluded.

2.2. Outcomes, data analysis and risk of bias

The primary outcome in this meta-analysis was the rate of clinical cure in patients with pneumonia caused by MSSA. No subgroup analysis was planned due to the expected low sample size. Risk differences (RDs) with 95% confidence intervals (CIs) were estimated using random-effects models, and heterogeneity (I^2) was assessed using Cochran’s χ^2 test. Study quality was evaluated independently by two authors (KE and AA) using the Cochrane risk of bias tool for RCTs (low, unclear or high) [15]. Funnel plot was not used to examine small-studies effects owing to the small number of studies. Comprehensive Meta-Analysis v.3 software (Biostat Inc., Englewood, NJ) was used for all analyses.

3. Results

The search process identified 337 articles and a total of 5 RCTs met the inclusion criteria [16–20] (Fig. 1). The characteristics of the five included studies are provided in Table 1. Four studies included adults [16–19] and one study included paediatric patients [20]. Four RCTs used ceftaroline [16,17,19,20], whilst one used ceftobiprole [18]. The studies were conducted between 2006–2014 and were non-inferiority double-blind [16–18] (except one superiority, observer-blind [20]) RCTs funded by drug companies that manufacture the newer cephalosporins. Clinical cure was consistently defined among all of the included studies as total resolution of all signs and symptoms of pneumonia or improvement to such an extent that no further antimicrobial therapy was necessary. Four studies were multicontinental [16–18,20] and one study was conducted in Asia [19]. For ceftriaxone adult dosing, two of the RCTs used 2 g q24h [18,19], whilst two used 1 g q24h [16,17]. The adult studies included patients from several continents with a mean age of between 53 years and 61 years who were not admitted to intensive care units and who had mild-to-moderate community-acquired pneumonia (CAP). Only one study allowed empirical atypical coverage with clarithromycin for the first day [16].

Clinical cure with ceftriaxone was statistically lower (RD, −28.5%, 95% CI −53.5% to −3.4%; $P = 0.026$; $I^2 = 16.321\%$; $Q = 4.780$; $P = 0.136$) than with ceftaroline or ceftobiprole (Fig. 2). An assessment of study quality is provided in Table 2.

4. Discussion

A meta-analysis provides the opportunity to detect a statistically significant difference that might not be detected by a single trial, particularly if that trial includes a small sample size. This meta-analysis showed, with low heterogeneity, that ceftriaxone use was associated with higher clinical failure compared with ceftaroline or ceftobiprole in patients with CAP caused by MSSA. These findings support existing evidence of the suboptimal impact of ceftriaxone in treating MSSA infections and raise concern about whether ceftriaxone is the optimal β-lactam for empirical therapy of CAP.

A previous survey reported that 71% of infectious diseases physicians would use ceftriaxone for osteoarticular infections caused by MSSA, however more than one-half of them would use it infrequently [21]. Previously published comparative studies were all observational in design and likely included more stable and less sick patients in the ceftriaxone group [9]. A 2011 study reported a higher 30-day mortality rate in patients with MSSA bacteraemia treated with third-generation cephalosporins (ceftriaxone and cefotaxime) compared with those treated with cloxacillin or cefazolin (194 patients vs. 131 patients, respectively; $P = 0.008$) [22]. A 2012 study of 124 patients found no significant difference between ceftriaxone and oxacillin in treatment success for osteoarticular infections caused by MSSA [23]. A 2013 study of 122 patients with MSSA infection, the majority with osteomyelitis or bacteraemia, found that favourable clinical outcome rates were similar between ceftriaxone and cefazolin [24]. A 2014 study then compared ceftriaxone with standard-of-care therapy (nafcillin, cefazolin or vancomycin) in the treatment of MSSA bacteraemia and demonstrated that there were no significant differences in clinical outcomes. However, one-quarter of patients in the standard-of-care group received vancomycin, which is less effective than standard antistaphylococcal agents [25]. Finally, a 2018 study of 71 MSSA bacteraemia patients observed a higher rate of failure with ceftriaxone compared with cefazolin ($P = 0.028$) [26].

Most studies included in this meta-analysis did not use empirical atypical bacterial coverage, which is recommended for CAP [27]. It is not clear whether empirical macrolides could reduce clinical failure in CAP caused by MSSA as they have some MSSA activity in addition to their anti-inflammatory effects. However, a retrospective study found poor outcomes with ceftriaxone with or without azithromycin for the treatment of MSSA CAP [28]. In addition, it is not clear whether pharmacokinetic characteristics, such as lower penetration of ceftriaxone into lung tissues or extensive protein binding resulting in decreased free unbound fraction of the drug, might have contributed to reduced clinical efficacy [29]. In a

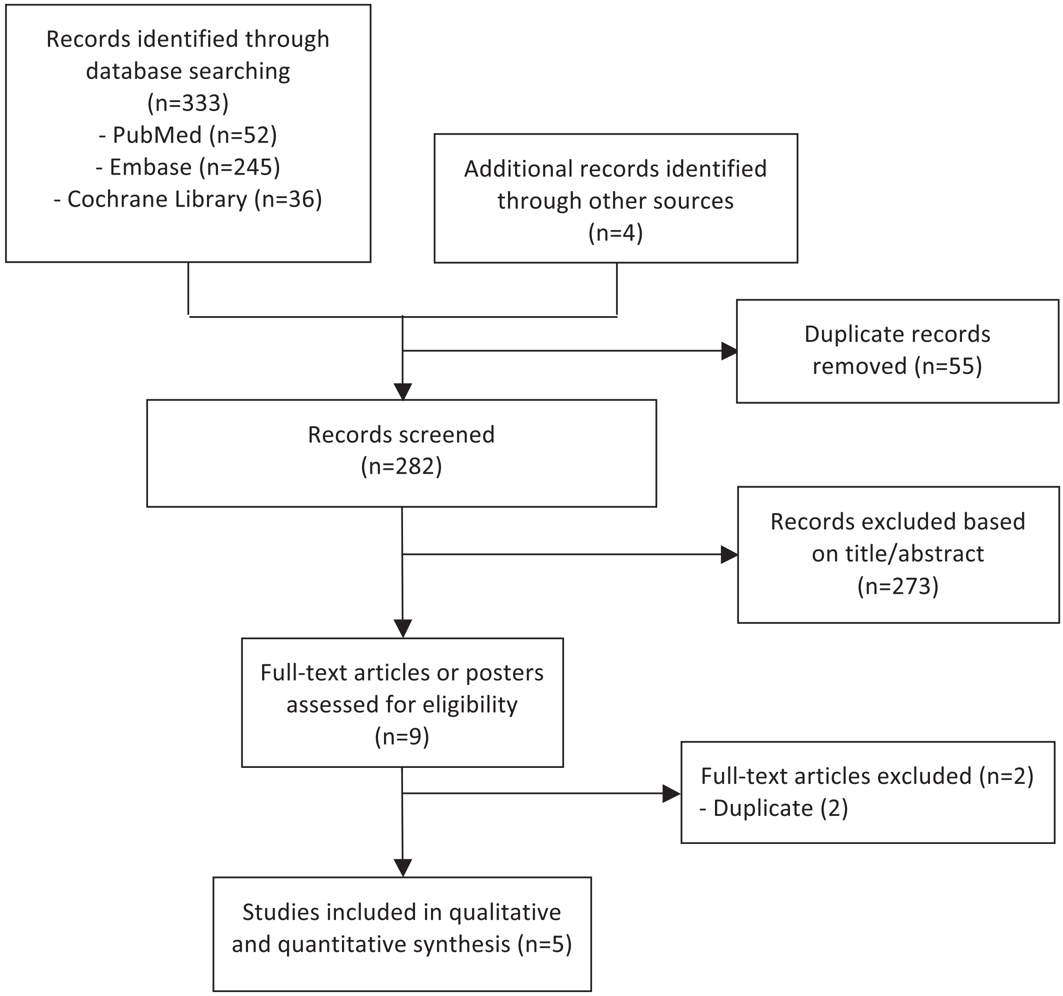

Fig. 1. Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.

Table 1
Characteristics of the included studies.

Study	Study period	Design	Location	Funding source (manufactured drug)	Enrolled patients	Mean age (years)	Patient characteristics	Ceftriaxone vs. new cephalosporins	Atypical bacteria coverage	Duration of therapy (days)
File Jr et al., 2011 [16]	2008	Non-inferiority, double-blind, RCT	114 sites in Asia, Africa, Europe, Latin America and USA	Industry (ceftaroline)	13 vs. 10	61	Non-ICU patients with mild-to-moderate CAP	Ceftriaxone 1 g i.v. q24h vs. ceftaroline 600 mg i.v. q12h	Clarithromycin 500 mg orally q12h for 24 h	5–7 (max. 7)
Low et al., 2011 [17]	2007–2008	Non-inferiority, double-blind, RCT	84 sites in Asia, Europe and Latin America	Industry (ceftaroline)	15 vs. 15	61	Non-ICU patients with mild-to-moderate CAP	Ceftriaxone 1 g i.v. q24h vs. ceftaroline 600 mg i.v. q12h	No	5–7 (max. 7)
Nicholson et al., 2012 [18]	2006–2007	Non-inferiority, double-blind, RCT	103 sites worldwide	Industry (ceftobiprole)	6 vs. 6	53	Mild-to-moderate CAP (unclear ICU status)	Ceftriaxone 2 g i.v. q24h vs. ceftobiprole 500 mg i.v. q8h	No	3–7 (max. 14)
Zhong et al., 2015 [19]	2011–2013	Non-inferiority, double-blind, RCT	64 sites in Asia	Industry (ceftaroline)	4 vs. 4	55	Non-ICU patients with mild-to-moderate CAP	Ceftriaxone 2 g i.v. q24h vs. ceftaroline 600 mg i.v. q12h	No	5–7
Blumer et al., 2016 [20]	2013–2014	Superiority, observer-blind, RCT	11 sites in USA and Europe	Industry (ceftaroline)	1 vs. 3	4 (paediatrics)	Complicated CAP	Ceftriaxone 35.5 mg/kg i.v. q12h vs. ceftaroline 10–15 mg/kg i.v. q24h	No	7.5 vs. 9

RCT, randomised controlled trial; ICU, intensive care unit; CAP, community-acquired pneumonia; i.v., intravenous; q24h, every 24 h; q12h, every 12 h; q8h, every 8 h.

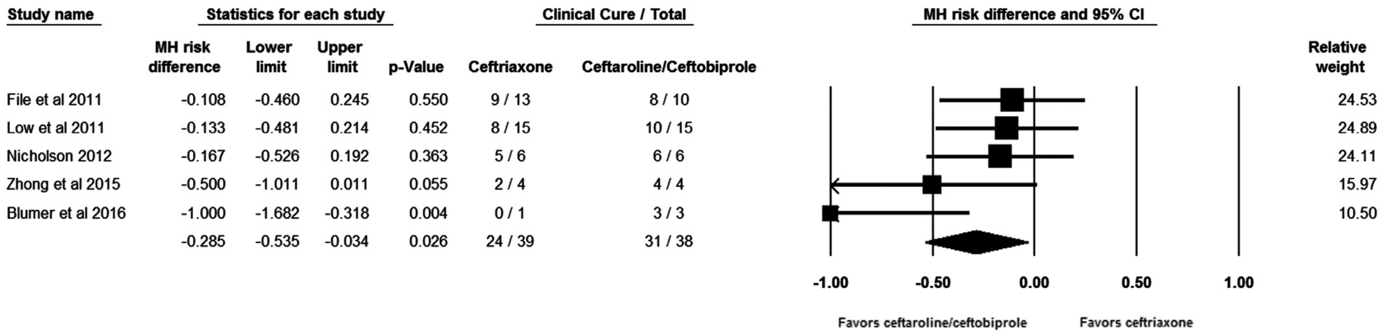

Fig. 2. Forest plot showing the risk difference of clinical cure in patients receiving ceftriaxone versus ceftaroline or ceftobiprole. Squares, risk difference; horizontal line, 95% confidence interval (CI); diamond, pooled risk difference.

Table 2
Quality assessment of included studies.

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
File et al., 2011 [16]	+	–	+	+	+	+	?
Low et al., 2011 [17]	+	–	+	+	+	+	?
Nicholson et al., 2012 [18]	+	?	+	+	+	+	?
Zhong et al. 2015 [19]	+	+	+	+	+	+	?
Blumer et al., 2016 [20]	+	+	–	+	+	+	?

+, low risk of bias; ?, unclear risk of bias; –, high risk of bias.

recent in vitro pharmacodynamic model of two MSSA clinical isolates with minimum inhibitory concentrations (MICs) of $\geq$2 μg/mL, it was found that ceftriaxone was significantly less active than ceftaroline even with higher doses of 2 g every 12 h, and this was assuming bronchial epithelial lining fluid (ELF) penetration of 100% [12]. Ceftriaxone ELF exposure is lower than that assumed, which would result in more reduced activity.

This meta-analysis has some limitations. We could not compare ceftriaxone with standard antistaphylococcal agents because there are no RCTs comparing these two groups as ceftriaxone is typically used empirically for its broader spectrum of activity, whilst cefazolin is studied empirically for infections caused by Gram-positive bacteria. However, we believe that we can extrapolate the findings from studies using newer cephalosporins to standard antistaphylococcal agents as both have more potent antistaphylococcal activity than ceftriaxone. Another limitation is the small number of studies and the small sample size within the studies. None the less, the meta-analysis was able to find a statistically significant difference in clinical success. All of the included studies were funded by manufacturing companies, which can result in sponsorship bias. Two included studies used a ceftriaxone dose of 1 g/day, but it is unclear whether this dose is sufficient for such patients. However, a major strength of this study was that it included data from double-blind RCTs, which reduces the risk of bias. Another strength is that the definitions of clinical cure were consistent among the included studies.

These findings add to the current limited data and encourage future research to compare ceftriaxone with cefazolin and other standard antistaphylococcal agents and to explore whether ceftriaxone dosage has an impact on clinical outcomes. It worth mentioning that a recent aetiology study in five hospitals in Chicago and Nashville (USA) found that *S. aureus* was the second most common typical bacterial cause of CAP in adults requiring hospitalisation, after *Streptococcus pneumoniae* [30]. Institutions having a higher prevalence of MSSA causing pneumonia might want to consider alternative empirical therapy. Until more data are published, we recommend against using ceftriaxone for the treatment of MSSA infections, particularly MSSA pneumonia.

In conclusion, the results of this meta-analysis demonstrate that ceftriaxone use is associated with higher clinical failure compared with ceftaroline or ceftobiprole in patients with CAP caused by MSSA. In the future, large RCTs should be conducted to evaluate ceftriaxone efficacy compared with standard antistaphylococcal agents in the treatment of MSSA infections. However, the current results support the notion that ceftriaxone is not a preferred agent for the treatment of MSSA infections. In addition, this is the first study showing poor response to ceftriaxone when used for MSSA pneumonia.

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Competing interests

None declared.

Ethical approval

Not required.

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