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REVIEW

Efficacy of Ceftriaxone 1 g daily Versus 2 g daily for The Treatment of Community-Acquired Pneumonia: A Systematic Review with Meta-Analysis

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ABSTRACT

Introduction: Ceftriaxone has been recommended as a first-line treatment for various infections; however, the doses for pneumonia have not been a consensus in randomized clinical trials. To compare ceftriaxone 1 g daily efficacy to other ceftriaxone dosing regimens in community-acquired pneumonia.
Area covered: We performed a systematic review and meta-analysis on PubMed, Web of Science, Scopus, and LILACS. Randomized controlled trials of ceftriaxone in community-acquired pneumonia were included. Outcomes included clinical cure in modified intention-to-treatment, clinically and microbiologically evaluable patients.
Expert opinion: Ceftriaxone dosages of 1 g daily are as safe and effective as other antibiotic regimens for community-acquired pneumonia. Twenty-four articles fulfilled the inclusion criteria. Twelve studies evaluated ceftriaxone regimens at a dosage of 2 g daily and 12 studies evaluated ceftriaxone at a dosage of 1 g daily. The odds-ratio of clinical cure in the modified intention-to-treatment patients administered either ceftriaxone (4666 patients) or a comparator (4411 patients) was 0.98 (95% CI [0.82–1.17]). Comparator regimens showed similar efficacy to ceftriaxone regimens of 1 g daily, with an odds ratio of 1.03 (95% CI [0.88–1.20]). Dosages higher than ceftriaxone 1 g daily did not result in improved clinical outcomes for community-acquired pneumonia patients (OR 1.02, 95% CI [0.91–1.14]).

ARTICLE HISTORY
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KEYWORDS
Ceftriaxone; Streptococcus pneumoniae; Antimicrobial stewardship; community-acquired pneumonia; dose

1. Introduction

Ceftriaxone is a strategically used antibiotic that has been recommended as a first-line treatment for various infections. Several randomized controlled trials (RCTs) have evaluated ceftriaxone's efficacy in the treatment of community-acquired pneumonia (CAP). However, the doses used in the RCTs have varied from 1 to 4 g daily. The dosing intervals also varied – from 1 to 2 infusions daily. These variations have been present since the beginning when Abbate et al. evaluated ceftriaxone's efficacy at 2 g daily and 1 g daily in the same trial [1]. In another study, 4 g daily was used for hospital-acquired pneumonia [2]. Even in the three most recent RCTs, which had the same sponsor, ceftriaxone dosages varied from 1 g daily in the first two studies, to 2 g daily in the third [3–5]. Interestingly, lower doses (<1 g) have been shown to achieve therapeutic targets. Efficacy has even been demonstrated at dosages as low as 250 mg [6].

Ceftriaxone pharmacokinetics/pharmacodynamics (PK/PD) studies have been published with variable findings. The severity of infection, degree of renal clearance, pathogen species and minimum inhibitory concentration (MIC) were the most frequently appearing contributors to PK/PD variance [7–9].

The first PK study with ceftriaxone was published in 1980 [10] and consisted of six healthy patients. The study demonstrated that a 500 mg IV regimen achieved therapeutic levels at 6 h and 30 h. Recent PK studies in patients with active pneumonia have also demonstrated the safety of ceftriaxone dosing at 1 g daily, including septic patients [11]. In severely ill patients, a 2 g ceftriaxone dosage has been demonstrated to achieve therapeutic levels for MICs below 2 mg/L [7].

With the exception of the PK/PD studies, there are no RCTs that compare ceftriaxone dosages. In this systematic review and meta-analysis, we indirectly compared the efficacy of ceftriaxone 1 g daily to other ceftriaxone dosing regimens in CAP patients.

2. Methods

2.1. Search strategy

Using PubMed, Web of Science, Scopus, and LILACS we searched for RCTs published in English, French, Spanish and Portuguese that compare the efficacy of ceftriaxone with different doses to comparators in the treatment of CAP. The search included studies from inception to November 2017. The keywords used were 'ceftriaxone' and 'pneumonia.' Results were divided into two groups: ceftriaxone 1 g daily versus comparators and ceftriaxone 2 g daily (1 g twice a day or 2 g daily) versus comparators. This systematic review followed PRISMA statement guidelines.

2.2. Data extraction and quality evaluation

Two reviewers independently screened all studies based on either title or abstract for eligibility. Discrepancies were

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Article Highlights

- Pneumonia is one of the top infectious diseases related to death and correct management usually needs antimicrobial prescription. Unfortunately, there are few evidences of correct ceftriaxone dose regimens (1 g q24h, 1 g q12h or 2 g q24h).
- Antimicrobial resistance is rapidly increasing, and stewardship programs aim to encourage rational antibiotic usage. Therapeutic decision according ceftriaxone dosage may play an important role on decrease selective pressure.
- S. pneumoniae is the most isolated pathogen on pneumonia and in vitro or pk-pd studies demonstrate possibility of ceftriaxone 1 g q24h regimen since pneumococcal MIC is usually achieved with safety.
- None RCT compared different ceftriaxone regimens to each other. Thus, there is a lack in literature about ceftriaxone regimens and its clinical applicability.
- This systematic review and meta-analysis compared different ceftriaxone dosages with comparators and evaluated clinical and microbiologic cure rates (including analysis per pathogens).

resolved through discussion. The reviewers then independently extracted the relevant data from all the RCTs to include in the meta-analysis. Discrepancies were evaluated by a third reviewer. In addition, the reviewers independently evaluated the methodological quality of each RCT using the Modified Jadad Scale [12].

2.3. Inclusion and exclusion criteria

Inclusion criteria were RCTs that compared different treatment regimens for CAP with at least one of those regimens being ceftriaxone treatment. Exclusion criteria were all non-randomized and non-clinical controlled trials, and RCTs that failed to differentiate between nosocomial pneumonia, CAP, and nursing home-acquired pneumonia. Any study including critically ill patients was excluded.

2.4. Definitions and outcomes

Diagnosis of CAP was based on clinical, laboratory, and x-ray findings. The Intention-To-Treat Group included all randomized patients, even if they had not received ceftriaxone as an initial therapy. The Modified Intention-To-Treat (mITT) Group consisted of patients who received at least one dose of a treatment regimen. The Clinically Evaluated (CE) Group included patients who had completed the study protocol and could, therefore, be evaluated. The Microbiologically Evaluated (ME) Group consisted of patients who submitted cultures after showing clinical improvement. The terms 'treatment successes' and 'favorable outcomes' were defined as clinical improvements in the mITT and CE groups, and as negative cultures in the ME group at the end of protocols.

A 'clinical cure' was defined as a total resolution of all pneumonia signs and symptoms, or an improvement of signs and symptoms to such an extent that no further antimicrobial therapy was necessary. Secondary outcomes such as mortality, incidence of adverse events, serious adverse events, and discontinuation due to adverse events were not evaluated.

2.5. Statistical analysis

All statistical analyses were performed with Review Manager Version 5.3. Dichotomous data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity among studies was assessed via a χ^2 test (chi-squared, where $p < 0.10$ indicates significant heterogeneity) and the I^2 (degree of heterogeneity) statistic. Publication bias was assessed via visual inspection of the funnel plot.

3. Results

3.1. Selected articles

Eight hundred and fifty articles were initially found using the search criteria. After title and abstract reviews, only 24 articles fulfilled the inclusion criteria (Figure 1). The first study was published in 1986, and the last in 2015. Ceftriaxone regimens, inclusion criteria, pneumonia severity indexes (PSI/PORTs), CURB scores, pneumonia classifications, and clinical and microbiological outcomes were evaluated.

3.2. Characteristics of selected RCTs

Nine hundred and sixteen patients met the criteria for mITT, 7442 for CE, and 2758 for ME. The mean Jadad score was 2.83 (range: 0–5). The low Jadad score appears to have been heavily influenced by early RCTs, which failed to contain sufficient study method descriptions. Table 1 shows all RCTs selected for this study.

Six studies evaluated ceftriaxone regimens at a dosage of 2 g daily [5,13–17], six studies evaluated ceftriaxone at a dosage of 1 g twice a day [18–23] and 12 studies evaluated ceftriaxone at a dosage of 1 g daily [1,3,4,24–32]. Inclusion criteria for CAP (clinical, laboratory, and x-ray findings) were present in all studies. PORT/PSI scores were used in 11 studies. Any study including critically ill patients was excluded. Only two RCTs adjusted ceftriaxone dosages according to patient renal

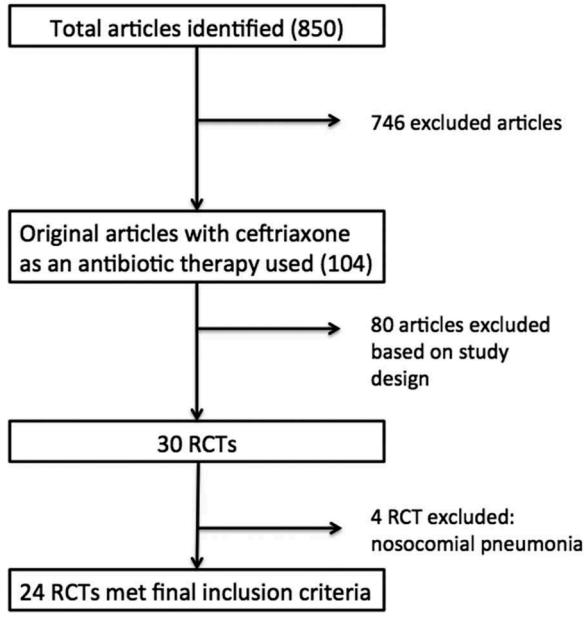

Figure 1. Search strategy.

Table 1. RCTs included in the systematic review with meta-analysis of community-acquired pneumonia.

Author	Year	Comparator	Jadad	CE	MR	mITT	Duration of antibiotic	Severity Score
Ceftriaxone 1g q12h								
Talaie et al.	2008	Cefepime 1g q12h	5	Yes	Yes	Yes	5–7 days	None
San Pedro et al.	2002	Linezolid 600mg q12h	2	Yes	Yes	Yes	7–14 days	None
Grossman et al.	1999	Cefepime 2g q12h	2	Yes	Yes	Yes	3–14 days	None
Zervos et al.	1998	Cefepime 2g q12h	2	Yes	Yes	Yes	5–10 days	None
Dansey et al.	1992	Cefotaxima 1g q12h	0	Yes	Yes	Yes	Minimum 5 days	None
Bittner et al.	1986	Cefamandole 1,5g q6h	0	Yes	Yes	Yes	15 days	None
Ceftrixona 1g 1q24h								
Abbate et al.	*1986*	Cefotaxime 2g q12h	0	Yes	Yes	Yes	7–12 days	None
de Klerk et al.	1999	Cefuroxime 1500mg q8h	2	Yes	Yes	Yes	Until 16 days	None
Frank et al.	2002	Levofloxacin 500mg q24h	2	Yes	Yes	Yes	10 days	PSI
Lode et al.	2002	Gemifloxacin 320mg q24h	2	Yes	Yes	Yes	7–14 days	PSI
Ortiz-Ruiz et al.	2002	Ertapenen 1g q24h	5	Yes	Yes	Yes	10–14 days	PSI
Vetter et al.	2002	Ertapenen 1g q24h	0	Yes	Yes	Yes	10–14 days	PSI
Woods et al.	2003	Ertapenen 1g q24h	5	Yes	Yes	Yes	10–14 days	PSI
Zervos et al.	2004	Levofloxacin 500mg q24h	2	Yes	Yes	Yes	7–14 days	PSI
Ortiz-Ruiz et al.	2004	Ertapenen 1g q24h	5	Yes	Yes	Yes	10–14 days	PSI
Paladino et al.	2007	Cefepime 1g q24h	3	Yes	Yes	No	10–14 days	None
File et al.	2011	Ceftaroline 600mg q12h	5	Yes	Yes	Yes	5–7 days	PSI
Low et al.	2011	Ceftaroline 600mg q12h	5	Yes	Yes	Yes	5–7 days	PSI
Ceftriaxona 2g q24h								
Zhong et al.	2015	Ceftaroline 600mg q12h	5	Yes	Yes	Yes	5–7 days	PSI
Nicholson et al.	2012	Ceftobiprole 500mg q8h	4	Yes	Yes	Yes	5–7 days	PSI
Petermann et al.	2001	Clinafloxacin 200mg q24h	2	Yes	Yes	Yes	7–21 days	APACHE
Pertel et al.	2008	Daptomycin 4mg/Kg q24h	4	Yes	Yes	Yes	7–14 days	PSI
Torres et al.	2008	Moxifloxacin 400mg q24h	5	Yes	Yes	Yes	7–14 days	PSI
Welte et al.	2005	Moxiloxacin 400mg q24h	0	Yes	Yes	Yes	7–14 days	PSI

CE: Clinically evaluable; MR: Microbiological Response; mITT: modified Intention-to-treat;
PSI: Pneumonia severity index; APACHE: Acute physiology and chronic health evaluation.

clearance abilities [5,32]. Duration of antimicrobial therapy ranged from 1 to 3 weeks. Six studies utilized a 1-week duration, 17 studies utilized a 1–2-week duration, and 1 study utilized a 3-week duration of therapy.

3.3. Modified intention-to-treat (miTT) group

The antibiotic regimen outcomes for CAP were similar in the mITT Group. The OR of clinical cure in the 9077 mITT patients administered either ceftriaxone (4666 patients) or a comparator (4411 patients) was 0.98 (95% CI [0.82–1.17], see Figure 2). The largest RCT had a weight influence of 6.6%. The majority of RCTs did not show a statistical difference between the comparator and ceftriaxone groups. Exceptions were Zhong et al. [5], Talaie et al. [18], and Zervos et al. [20]. In two of the studies, the comparators (cefepime and levofloxacin) were both inferior to ceftriaxone, but Zhong et al. reported an inferior outcome in ceftriaxone at 2 g daily when compared to ceftaroline at 600 mg twice a day [5] with an OR of 1.98 (95% CI [1.42–2.75]).

Comparator regimens showed similar efficacy to ceftriaxone regimens of 1 g daily, with an OR of 1.03 (95% CI [0.88–1.20], see Figure 3). Furthermore, dosages higher than ceftriaxone 1 g daily did not result in improved clinical outcomes for CAP patients. Figure 4 shows the Comparator Regimens Group compared to the Ceftriaxone 2 g daily (1 g twice a day or 2 g daily) Group, and no statistically significant difference was found between the two (OR 1.02, 95% CI [0.91–1.14]).

3.4. Clinically evaluated (CE) group

Comparator regimens for CAP did not display superiority in the CE group when compared to all ceftriaxone groups together (OR 1.00, 95% CI [0.88–1.14]), 7494 patients (3872 from comparator and 3622 from ceftriaxone), see Figure 5. The largest RCT, by Pertel et al., had a weight influence of 20.8%, with an OR of 0.34 (95% IC [0.23–0.49]) in favor of ceftriaxone compared to daptomycin [15]. However, no statistical difference was found between comparator and ceftriaxone regimens for the majority of the RCTs, although three studies showed a favorable response to comparator regimens [3–5]. All three studies evaluated ceftaroline as the comparator versus ceftriaxone at 1 or 2 g daily (Figures 6 and Figure 7).

Few studies evaluated separately patients classified as PORT V [13]. Only 1 study used ceftriaxone 1 g q24h compared to ertapenem 1 g q24h with clinical cure rates of 90% (9/10) and 70% (9/13), respectively. Other three studies evaluated ceftriaxone 2 g *per* day *versus* comparator regimens with clinical cure rates of 87% (90/103) and 85% (76/89), respectively [30].

3.5. Microbiologically evaluated group (ME)

In the ME group, no statistical difference was found between comparator and ceftriaxone regimens (ceftriaxone dosages of 1 g daily and 2 g daily), with an OR of 0.94 (95% CI [0.75–1.19]). The ME group consisted of 2758 patients, with 1439 having received comparators and 1319 having received ceftriaxone (Figure 8). Similar statistical results were observed in the RCT group between ceftriaxone 1 g daily and ceftriaxone 2 g daily (Figures 9 and 10).

S. pneumoniae was the microorganism isolated on 1458 patients. Seven hundred and forty-two were treated with ceftriaxone and 716 with comparator regimen. Similar cure rates were found among different regimens. Ceftriaxone 1 g q24h and comparator groups clinical cure rates were 86.7% (308/355) and 89% (291/327) ($P = 0.4$). Clinical cure rates in patients with

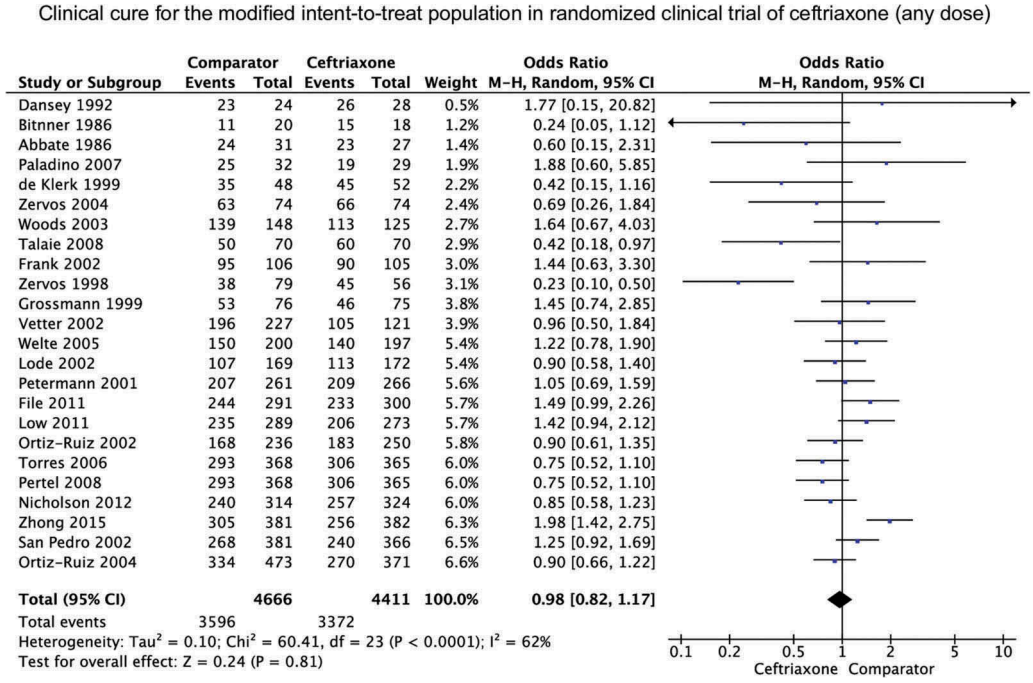

Figure 2. Odds ratios (ORs) of clinical cure for the modified intent-to-treat population in randomized clinical trial of ceftriaxone (any dose) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

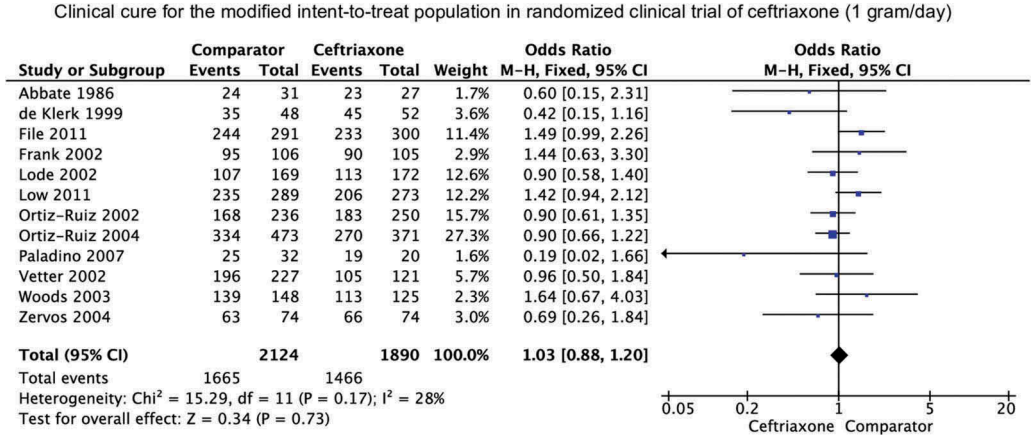

Figure 3. Odds ratios (ORs) of clinical cure for the modified intent-to-treat population in randomized clinical trial of ceftriaxone (1 gram/day) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

ceftriaxone 1 g q12h and comparator groups were 91.9% (80/87) and 90% (76/84), respectively (*P= 0.79*). On ceftriaxone 2 g q24h and comparator groups, clinical cure rates were 89% (269/300) and 84% (257/305), respectively. Statistical analysis did not demonstrate differences *(P = 0.054)*. Overall, clinical cure rates between all ceftriaxone regimens and comparators were 88% and 87%, respectively (*P = 0.42*).

H. influenzae was isolated on 337 patients. From these, 169 were treated with ceftriaxone and 168 with comparator regimen. Similar cure rates were found among different regimens. On ceftriaxone 1 g q24h and comparator groups clinical cure rates were 92% (108/117) and 89% (109/122), respectively *(P = 0.5)*. On ceftriaxone 1 g q12h and comparator groups, clinical cure rates were 100% for both regimens and 12 patients each. On ceftriaxone 2 g q24h and comparator groups, clinical cure rates were 90% (36/40) and 94% (32/34) *(P = 0.68)*. Overall, clinical cure rates between all ceftriaxone regimens and comparators were 92% and 91%, respectively *(P = 0.69)*.

S. aureus was isolated on 222 patients. From these, 106 were treated with ceftriaxone and 116 with comparator regimen. On ceftriaxone 1 g q24h and comparator groups clinical cure rates were 66% (37/56) and 84% (49/58), respectively. Statistical analysis demonstrates significant differences [OR = 2.79; 95%IC 1.13–6.48 *(P = 0.025)*]. On ceftriaxone 1 g q12h and comparator groups, clinical cure rates were 100% (7/7) and 90% (9/10), respectively *(P = 1.0)*. On ceftriaxone 2 g q24h and comparator groups, clinical

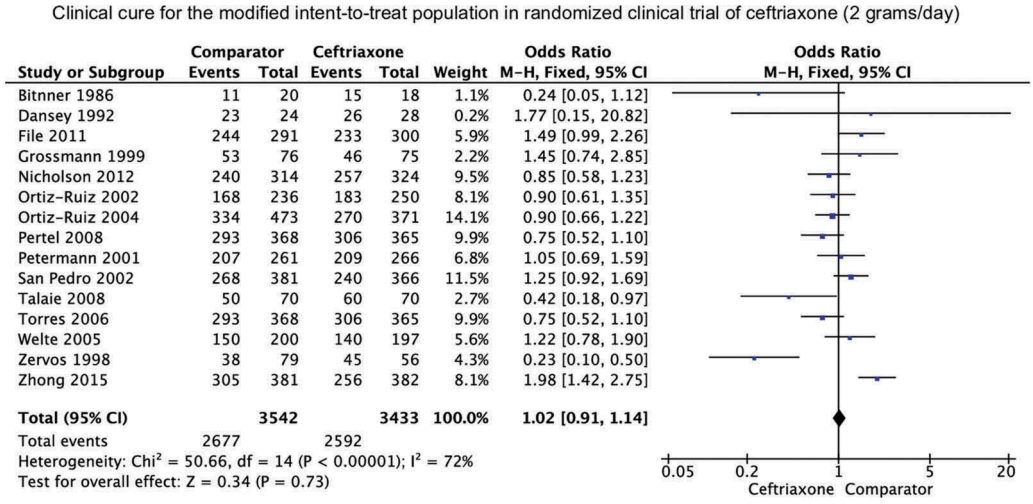

Figure 4. Figure 3. Odds ratios (ORs) of clinical cure for the modified intent-to-treat population in randomized clinical trial of ceftriaxone (2 grams/day) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

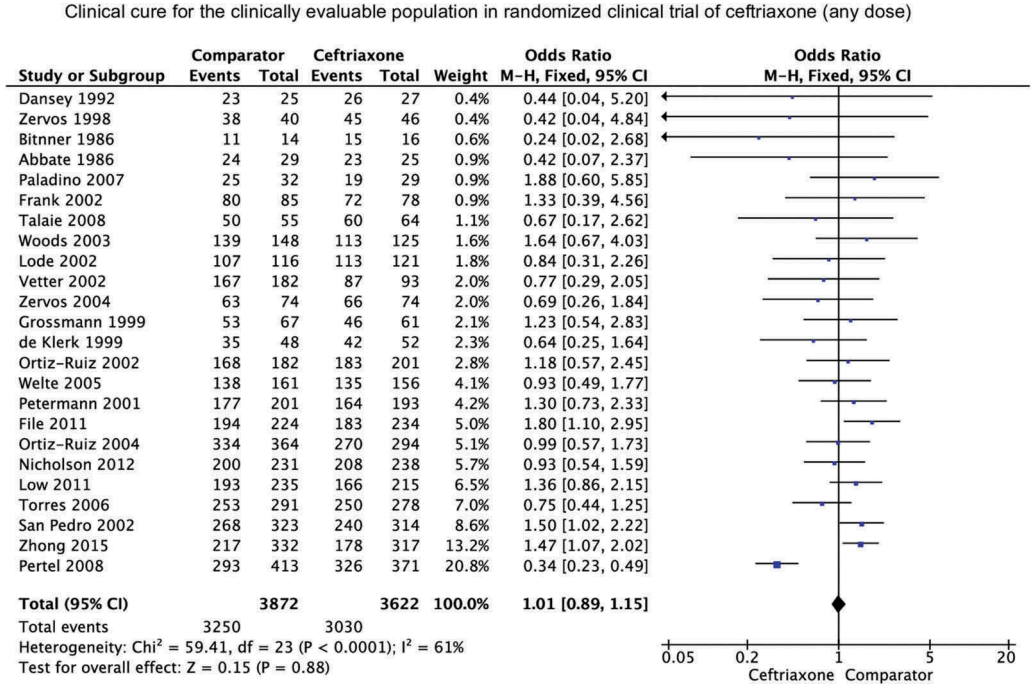

Figure 5. Odds ratios (ORs) of clinical cure for the clinically evaluable population in randomized clinical trial of ceftriaxone (any dose) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

cure rates were 81% (35/43) and 79% (38/38), respectively *(P = 1.0)*. Overall, clinical cure rates between all ceftriaxone regimens and comparators were 74% and 82%, respectively *(P = 0.14)*.

3.6. Publication bias

Publication bias was analyzed by funnel plot graphics. Bias was significantly observed in the mITT group. The CE and ME groups displayed less bias. Bias was found to be particularly low in the ME group (Figure 11).

4. Discussion

The World Health Organization Collaborating Centre for Drug Statistics Methodology has determined that ceftriaxone's defined daily dose (DDD) is 2 g. However, CAP treatment regimens vary considerably. Unfortunately, no RCTs have examined ceftriaxone dose variance. In this meta-analysis, we compared the efficacy between ceftriaxone dosages of 1 g daily and 2 g daily by assessing all RCTs that specifically utilized ceftriaxone to treat CAP. Our results showed no statistically significant difference between ceftriaxone and

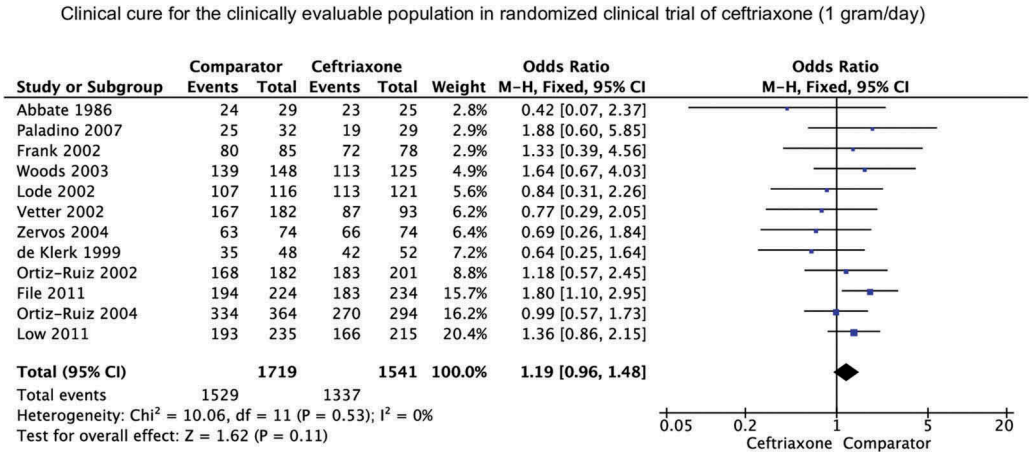

Figure 6. Odds ratios (ORs) of clinical cure for the clinically evaluable population in randomized clinical trial of ceftriaxone (1 gram/day) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

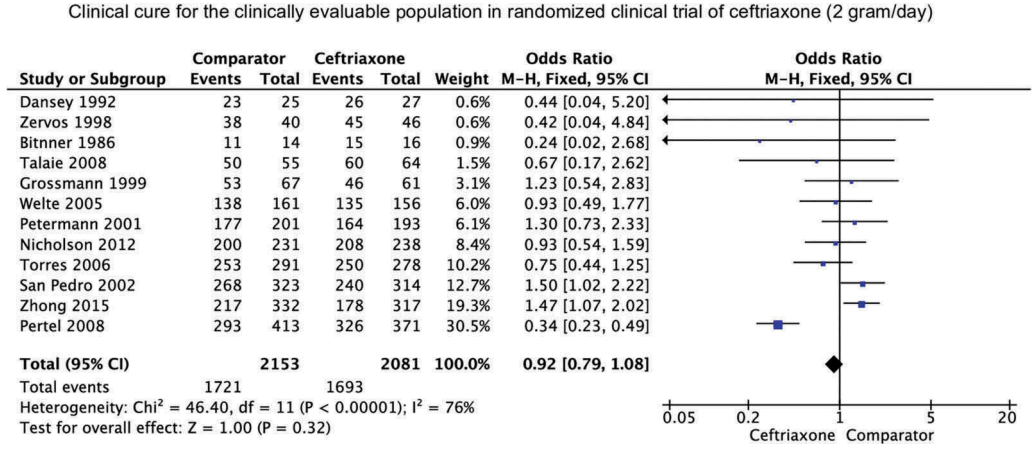

Figure 7. Odds ratios (ORs) of clinical cure for the clinically evaluable population in randomized clinical trial of ceftriaxone (2 gram/day) in community-acquired pneumonia. Vertical line = the no difference point between the 2 regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

comparator regimens for CAP treatment (OR 0.97, 95% CI [0.81–1.16]). Among the studies we reviewed, only one (Zhong et al.) showed a statistically significant difference between ceftriaxone and a comparator, in favor of the comparator regimen (ceftaroline at 600 mg twice a day) [5].

The first two RCTs (Focus 1 and Focus 2) evaluated ceftaroline 600 mg twice a day compared to ceftriaxone 1 g daily for CAP [3,4]. The outcomes favored ceftaroline with a number necessary to treatment (NNT) of 11.9 and 20, for Focus Groups 1 and 2, respectively. When 2 g ceftriaxone was utilized as the control, the NNT in favor of ceftaroline dropped slightly to 11.7, which was not significant in the most severe patients (PORT Risk Class IV).

In this meta-analysis, comparator regimens did not display superiority to ceftriaxone 1 g daily in the mITT (OR 1.03, 95% CI [0.88–1.20]), CE (OR 1.19, 95% CI [0.96–1.48]), or ME group (OR 1.11, 95% CI [0.80–1.53]). Two RCTs included 43.7% of all patients in the CE 1 g analysis, which greatly influenced our meta-analysis in this subgroup results but not in other analysis [27,28].

It was also evaluated efficacy of different regimens *per* pathogens. CAP caused by *S. pneumoniae* and *H. influenza* presented similar clinical cure rates to ceftriaxone and other regimens (ceftriaxone 1 g q24h, 1 g q12h, 2 g q24h *versus* comparators). *S. aureus* did not demonstrate significant differences on clinical cure rates to ceftriaxone 1 g q12h, 2 g q24 h *versus* comparators. However, ceftriaxone 1 g q24 h to *S. aureus* was inferior than comparator regimens *(P = 0.025)*. Possibly this result reflects ceftaroline higher binding affinity to *S. aureus* (MSSA and MRSA) [33] since two RCT included in this subanalysis used ceftaroline as comparator regimen [3,4].

The current meta-analysis has some limitations. First, only English, Portuguese, Spanish and French articles were analyzed, as well as only articles from PUBMED, Web of Science and SCOPUS were included, which may have created a selection bias. Second, results of Pertel et al. (2008) may contain a bias favoring ceftriaxone. This RCT compared daptomycin to ceftriaxone for CAP [15]. However, daptomycin is contra-indicated in pulmonary infections due to the pulmonary surfactant inhibition of daptomycin's bactericidal action

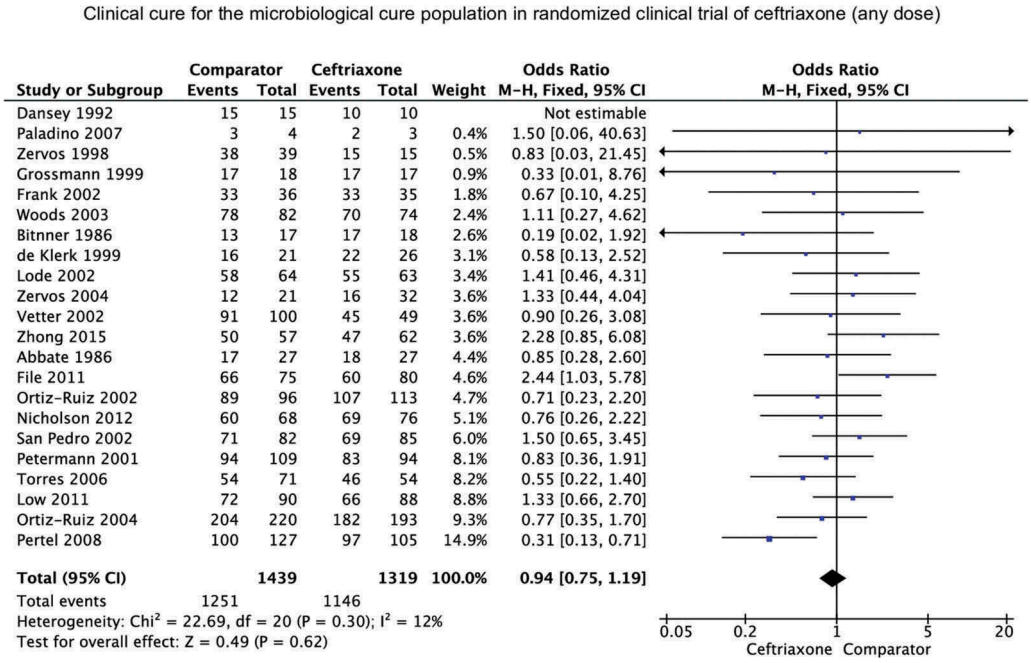

Figure 8. Odds ratios (ORs) of clinical cure for the microbiological cure population in randomized clinical trial of ceftriaxone (any dose) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

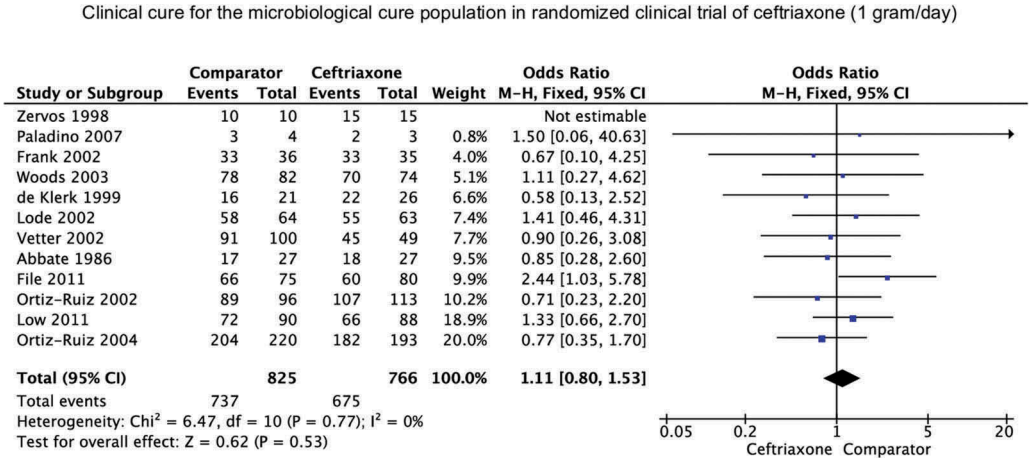

Figure 9. Odds ratios (ORs) of clinical cure for the microbiological cure population in randomized clinical trial of ceftriaxone (1 gram/day) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

[34]. Another limitation was the low Jadad manuscript scores (2.83 with I^2 = 63%). This was a result of the inclusion of older trials containing lower numbers of patients, large variances, and larger standard errors. The funnel plot demonstrated a discrete publication heterogeneity (due to older studies with small sample sizes and low statistical power). In addition, there are no RCTs that have compared different ceftriaxone doses for CAP. The first study included was published in 1986, and other studies were before 2000. There was improvement in medical care over 20 years, but these studies contributed with few patients.

Thus, we have examined a variety of comparators against a variety of ceftriaxone dosages. Other meta-analyses have utilized a similar method of comparison to examine the efficacy of cefepime against various comparators [35]. No head-to-head comparison was made. Our study has shown that in a majority of RCTs, ceftriaxone dosages of 1 g daily are as safe and effective as other antibiotic regimens. PK/PD models provide further support for the safety and efficacy of ceftriaxone at this dosage. All results of this meta-analysis must be cautiously considered. There is important heterogeneity of the data and a systematic review without meta-analysis could be

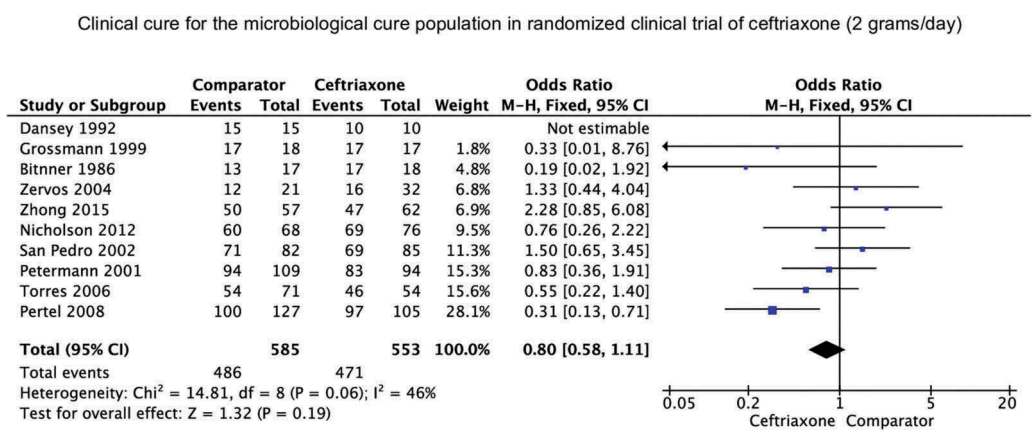

Figure 10. Odds ratios (ORs) of clinical cure for the microbiological cure population in randomized clinical trial of ceftriaxone (2 grams/day) in community-acquired pneumonia. Vertical line = the no difference point between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

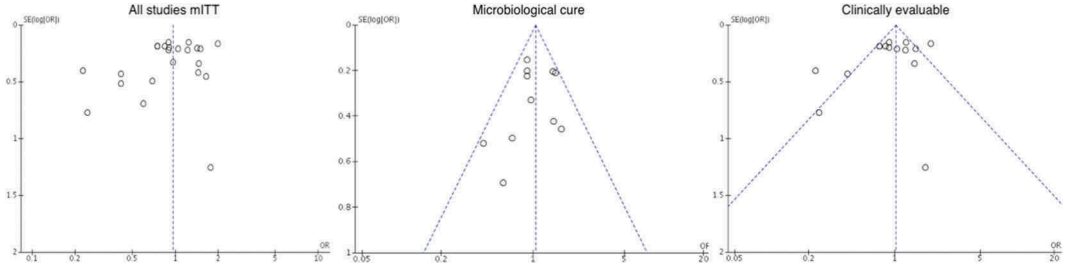

Figure 11. Funnet plot of publication bias: all studies mITT (left); microbiological cure (center); clinically evaluable patients (right).

more suitable; however, heterogeneity could not be assessed without this analysis.

5. Conclusion

Our systematic review and meta-analysis demonstrated that neither other antibiotic regimens, nor ceftriaxone higher doses than 1 g per day are needed to treat CAP. Similar outcomes were found between different ceftriaxone doses and other antibiotics therapies. Ideally, a large RCT should be conducted to compare the efficacy of various ceftriaxone dosing regimens.

6. Expert opinion

Lower respiratory tract infection was demonstrated to be on the top 10 mortality causes, even on high-income countries. Among them, community-acquired pneumonia is a major problem around the world, mainly by being a leading disease on patients hospital admission. Antibiotics are commonly overused on CAP, both in dosage and in time treatment.

During last decades it has been demonstrated continuous growing bacteria resistance. Betalactams, such as ceftriaxone, play an important role on it by its strong beta-lactamases induction [e.g. *Extended-Spectrum Beta-Lactamases* (ESBL)]. Sooner after ceftriaxone initial usage on 1980, first ESBLs were isolated and nosocomial infection outbreaks were noticed [36,37]. Selection pressure is highly linked with *i.* prolonged time of treatment, *ii.* higher antimicrobial spectrum and *iii.* higher antimicrobial doses. Thus, antimicrobial stewardship programs (ASP) are responsible to suit antibiotic usage analysing cost-effectiveness without impairing patients outcomes. Unfortunately, it is not uncommon ASP to suit misuse only of antibiotic regimens used to treat nosocomial infection (e.g. piperacillin-tazobactam, carbapenems, aminoglycosides) and ignore potential harm on misuse of antimicrobial regimens on community-acquired infections (e.g. ceftriaxone). Suiting ceftriaxone usage may be an alternative to reduce ambiental antimicrobial pressure and resistance, and even hospital costs (e.g. drug price, human resources, administration timing, and equipment).

Further researches with an appropriate methodological design are needed to establish head-to-head effectiveness on different ceftriaxone regimens on CAP. Differences regarding plasma protein concentration and volume distribution disturbance must be clarified. Patients on septic shock or hypoproteinemia tend to low faster antibiotic plasma concentration and may change relation of time above MIC, which in cephalosporin are expected to be at least 50–70%. Moreover, divergent opinion among infectious diseases specialists about ideal pharmacodynamic target on critical patients exists (e.g. double or quadruple t/MIC). Methodological design under these situations might be the unsolved problem regarding ceftriaxone and CAP. Besides it, possible bacteria increasing resistance among community is now being a real concern around the world, but differences and fails on pneumococcal surveillance forbid extrapolate

data to all countries and enhances the geographical strictly related resistance. Patients diagnosed with CAP, mainly those without hypoproteinemia and normal volume distribution, are eligible candidates to ceftriaxone 1 g per day during 5–7 days.

Even on immunocompromised patients, such as people living with HIV/aids (acquired immunodeficiency syndrome), *S. pneumoniae* is the major pathogen on CAP. Nevertheless, apprehension regarding ceftriaxone dosage and needs to antibiotic association also exist. Recently, a clinical trial concludes that, when compared to ceftriaxone monotherapy, macrolide association do not improve outcomes on this population [38].

Surprisingly, these RCTs subjects were never approached leading to a lack of information and probably an antibiotic overuse. In view of that new classes of antibiotics are rarely launched, better approaches regarding time of treatment and appropriate doses are urgently required. First, better pneumococcal surveillance resistance should be emphasized in all regions. Second, RCTs with different ceftriaxone doses analyzing different group characteristics (e.g. plasma protein level, volume disturbance, renal clearance, and t/MIC) should be designed. After careful researches, possible different recommendations from nowadays would be done on ceftriaxone dose and time of treatment, leading to a further sparing broad spectrum antimicrobials.

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