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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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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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...
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 $\chi^2$ 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 function.

Figure 1. Search strategy.
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], Talae 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 ceftazidime at 600 mg twice a day [5] with an OR of 1.98 (95% CI [1.42–2.75]).

Comparator regiments showed similar efficacy to ceftriaxone regiments 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 Regiments 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 regiments 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 7).

Few studies evaluated separately patients classified as PORT V [13]. Only 1 study used ceftriaxone 1 g q24h compared to etramen 1 g q24h with clinical cure rates of 90% (9/10) and 70% (9/13), respectively. Other three studies evaluated ceftaroline 2 g per day versus comparator regiments 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

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Comparator</th>
<th>Jadad</th>
<th>CE</th>
<th>MR</th>
<th>mITT</th>
<th>Duration of antibiotic</th>
<th>Severity Score</th>
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</thead>
<tbody>
<tr>
<td>Talae et al.</td>
<td>2008</td>
<td>Cefepime 1g q12h</td>
<td>S</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>None</td>
</tr>
<tr>
<td>San Pedro et al.</td>
<td>2002</td>
<td>Linezolid 600mg q12h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>None</td>
</tr>
<tr>
<td>Grossman et al.</td>
<td>1999</td>
<td>Cefepime 2g q12h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3–14 days</td>
<td>None</td>
</tr>
<tr>
<td>Zervos et al.</td>
<td>1998</td>
<td>Cefepime 2g q12h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5–10 days</td>
<td>None</td>
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<tr>
<td>Dansey et al.</td>
<td>1992</td>
<td>Cefotaxima 1g q12h</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Minimum 5 days</td>
<td>None</td>
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<tr>
<td>Bittner et al.</td>
<td>1986</td>
<td>Cefamandole 1.5g q6h</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>15 days</td>
<td>None</td>
</tr>
<tr>
<td><strong>Ceftriaxona 1g q12h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbate et al.</td>
<td>1986</td>
<td>Cefotaxime 2g q12h</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–12 days</td>
<td>None</td>
</tr>
<tr>
<td>de Klerk et al.</td>
<td>1999</td>
<td>Cefuroxime 1500mg q8h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Until 16 days</td>
<td>None</td>
</tr>
<tr>
<td>Frank et al.</td>
<td>2002</td>
<td>Levofloxacin 500mg q24h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Lode et al.</td>
<td>2002</td>
<td>Gemifloxacin 320mg q24h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Ortiz-Ruiz et al.</td>
<td>2002</td>
<td>Ertapenem 1g q24h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Vetter et al.</td>
<td>2002</td>
<td>Ertapenem 1g q24h</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10–14 days</td>
<td>PSI</td>
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<tr>
<td>Woods et al.</td>
<td>2003</td>
<td>Ertapenem 1g q24h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Zervos et al.</td>
<td>2004</td>
<td>Levofloxacin 500mg q24h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Ortiz-Ruiz et al.</td>
<td>2004</td>
<td>Ertapenem 1g q24h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>10–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Paladino et al.</td>
<td>2007</td>
<td>Cefepime 1g q24h</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>10–14 days</td>
<td>None</td>
</tr>
<tr>
<td>File et al.</td>
<td>2011</td>
<td>Ceftaroline 600mg q12h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5–7 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Low et al.</td>
<td>2011</td>
<td>Ceftaroline 600mg q12h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5–7 days</td>
<td>PSI</td>
</tr>
<tr>
<td><strong>Ceftriaxona 2g q24h</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zhong et al.</td>
<td>2015</td>
<td>Ceftaroline 600mg q12h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5–7 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Nicholson et al.</td>
<td>2012</td>
<td>Ceftepibrol 500mg q8h</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5–7 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Petermann et al.</td>
<td>2001</td>
<td>Cimafloxacin 200mg q24h</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–21 days</td>
<td>APACHE</td>
</tr>
<tr>
<td>Pertel et al.</td>
<td>2008</td>
<td>Daptomycin 4mg/kg q24h</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Torres et al.</td>
<td>2008</td>
<td>Moxifloxacin 400mg q24h</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>PSI</td>
</tr>
<tr>
<td>Welte et al.</td>
<td>2005</td>
<td>Moxifloxacin 400mg q24h</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7–14 days</td>
<td>PSI</td>
</tr>
</tbody>
</table>

CE: Clinically evaluable; MR: Microbiological Response; mITT: modified Intention-to-treat; PSI: Pneumonia severity index; APACHE: Acute physiology and chronic health evaluation.
Clinical cure for the modified intent-to-treat population in randomized clinical trial of ceftriaxone (any dose) in community-acquired pneumonia. Vertical line = no difference between the two regimens; square = OR; diamond = pooled OR for all randomized controlled trials; horizontal line = 95% confidence interval (CI).

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 q12h and comparator groups, clinical cure rates were 100% (12/12) and 90% (12/13), respectively (P = 0.34). On ceftriaxone 1 g q24h and comparator groups, clinical cure rates were 92% (118/128) and 89% (118/133), respectively (P = 0.27). On ceftriaxone 2 g q24h and comparator groups, clinical cure rates were 90% (12/13) and 91% (12/13), respectively (P = 0.81). 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 90% (36/40) and 88% (27/31), respectively (P = 0.23). On ceftriaxone 2 g q24h and comparator groups, clinical cure rates were 90% (36/40) and 92% (32/34), respectively (P = 0.68). Overall, clinical cure rates between all ceftriaxone regimens and comparators were 92% and 91%, respectively (P = 0.69).

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 = no difference 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 = no difference 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
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. influenzae 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.
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 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).
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. Beta-lactams, 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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