

# Comparative efficacy of azithromycin versus clarithromycin in combination with beta-lactams to treat community-acquired pneumonia in hospitalized patients: a systematic review

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## Abstract

**Objective:** The objective was to compare the efficacy of azithromycin and clarithromycin in combination with beta-lactams to treat community-acquired pneumonia among hospitalized adults.

**Methods:** Five databases (PubMed, Google Scholar, Trip, Medline, and Clinical Key) were searched to identify randomized clinical trials with patients exposed to azithromycin or clarithromycin in combination with a beta-lactam. All articles were critically reviewed for inclusion in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Results:** Seven clinical trials were included. The treatment success rate for azithromycin–beta-lactam after 10 to 14 days was 87.55% and that for clarithromycin–beta-lactam after 5 to 7 days of therapy was 75.42%. *Streptococcus pneumoniae* was commonly found in macrolide groups, with 130 and 80 isolates in the clarithromycin-based and azithromycin-based groups, respectively. The length of hospital stay was an average of 8.45 days for patients receiving a beta-lactam–azithromycin combination and 7.25 days with a beta-lactam–clarithromycin combination.

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**Conclusion:** Macrolide inter-class differences were noted, with a higher clinical success rate for azithromycin-based combinations. However, a shorter length of hospital stay was achieved with a clarithromycin–beta-lactam regimen. Thus, a macrolide combined with a beta-lactam should be chosen using susceptibility data from the treating facility.

### Keywords

Community-acquired pneumonia, azithromycin, respiratory tract infection, meta-analysis, macrolide, clarithromycin, beta-lactam, *Streptococcus pneumoniae*, susceptibility data

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### Introduction

Community-acquired pneumonia (CAP) is a common lower respiratory tract infection that is associated with high morbidity and mortality.<sup>1</sup> The World Health Organization has indicated that CAP is responsible for almost 3 million deaths annually.<sup>2</sup> Higher mortality rates occur in hospitalized patients (almost 6%–20%) depending on the disease severity and the treatment settings.<sup>3</sup> The high rate of antimicrobial resistance by *Streptococcus pneumoniae* has increased the rate of hospitalization due to CAP and made treating this infection increasingly complex.<sup>4,5</sup> In 2019, the Infectious Disease Society of America (IDSA) recommended the use of combination therapy for hospitalized patients with CAP.<sup>6</sup> The standard treatment regimens that were recommended for nonsevere inpatient CAP are a beta-lactam with a macrolide or fluoroquinolone monotherapy, and treatment regimens recommended for the severe inpatient CAP are a combination of beta-lactam/macrolide or beta-lactam/fluoroquinolone. Owing to the emerging resistance pattern of CAP pathogens, combination regimens are superior to monotherapy particularly in patients with severe CAP, and this was supported by several studies.<sup>7</sup> Because it is not clear which

combination therapy is the most effective, some studies have examined the efficacy of beta-lactam and a macrolide<sup>8</sup> and many have studied the outcomes of beta-lactam and a macrolide versus fluoroquinolone.<sup>9</sup> However, only a few studies have investigated the clinical outcomes of a specific macrolide (azithromycin or clarithromycin) in combination with a beta-lactam.<sup>10</sup> Macrolides have been shown to be effective against bacteria that cause lower respiratory tract infections.<sup>11</sup> Bacteriostatic antimicrobials work by reversibly binding to the P site on the 50S subunit of bacterial ribosomes, but at a higher concentration, they have bactericidal properties.<sup>12</sup> A clinical trial was performed in patients with severe CAP class IV using the Pneumonia Severity Index (PSI), and this trial showed that monotherapy with a beta-lactam was inferior to combination therapy using a beta-lactam with macrolides and that patients who received monotherapy had delayed clinical stability compared with the combination therapy.<sup>13</sup> Another study in a cohort setting was performed retrospectively using CAP patients with PSI class V, and this study showed better outcomes with a beta-lactam and macrolide combination compared with fluoroquinolone monotherapy.<sup>14</sup> Several studies with an observational design suggested that initial therapy with a

macrolide combined with a beta-lactam may reduce mortality rates and reduce the number of hospitalization days.<sup>15–17</sup>

Despite these previous studies, there are limited data on the macrolides inter-class differences when treating patients with CAP that might influence the choice of macrolide when availability is not a concern. The objective of this article is to systematically review the literature on the comparative efficacy of azithromycin and clarithromycin in combination with beta-lactams to treat patients with CAP among hospitalized adults and to evaluate the outcomes that are used to determine drug efficacy to provide clinical recommendations.

## Methods

### Eligibility criteria

To determine the eligibility criteria of this review, we developed a strategy using Population, Intervention, Comparison, Context, Outcome, Study Design

(PIC<sup>2</sup>OS) and determined the inclusion and exclusion criteria, which are listed in Table 1. Additionally, we included studies that were published in English only and that were published from 2000 to 2020. This was a systematic review, so ethics approval and patient consent were not required.

### Information source and search strategy

For the primary search, the reviewers (JAS and RKM) independently performed a comprehensive search of five databases (PubMed, Google Scholar, Trip, Medline, and Clinical Key) to identify the relevant studies. Only the full text studies were included. A manual search of the references cited by the relevant articles was performed as a secondary search strategy, as shown in Figure 1.

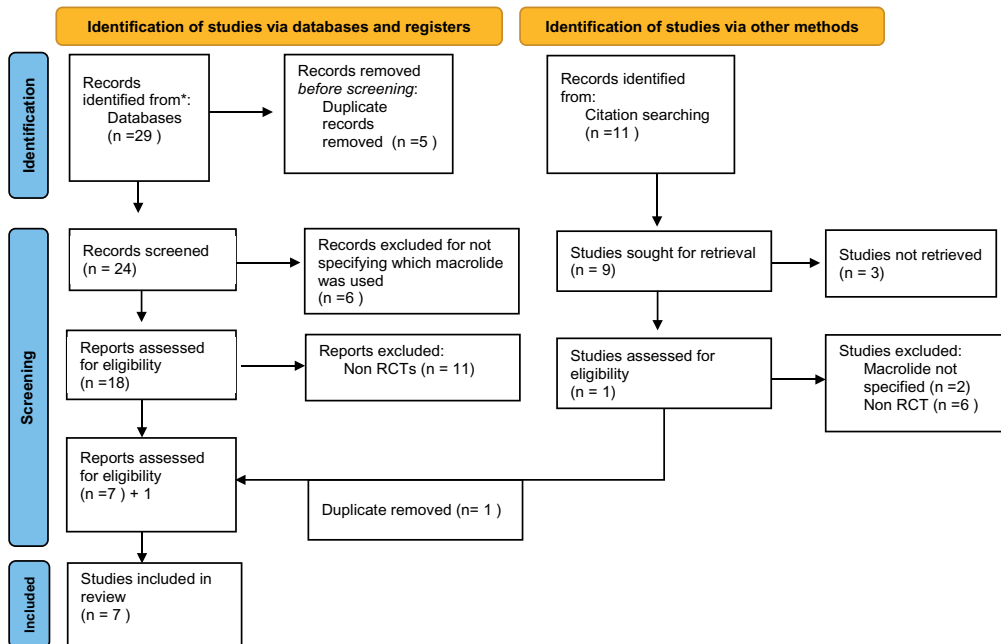
### Search

A highly sensitive search strategy was used, which included the following words

**Table 1.** Inclusion and exclusion criteria.

Eligibility criteria (PIC <sup>2</sup> OS)	Inclusion criteria	Exclusion criteria
Population	Patients diagnosed with community-acquired pneumonia	Patients diagnosed with ventilator-associated or hospital-acquired pneumonia
Intervention	Azithromycin or clarithromycin in combination with a beta-lactam	
Comparison	Compared with control group or other comparator	
Context	Hospitalized patients	Patients treated on an outpatient basis
Outcomes	Primary: Clinical success rate at the end of therapy Secondary: Length of hospital stay, mortality, morbidity, and days of clinical stability	
Study Design	RCT only	Systematic reviews, meta-analyses, single case studies, cross-sectional studies, qualitative studies, case reports, audits of guidelines, conference abstracts and letters to editors.

RCT, randomized controlled trial; PIC<sup>2</sup>OS, Population, Intervention, Comparison, Context, Outcome, Study Design.



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for the identified articles.

and medical subject heading (MeSH) terms: “azithromycin”, “clarithromycin”, community-acquired pneumonia”, “macrolides”, and “beta-lactam” while searching the selected data bases. Specified beta-lactams were also used to retrieve more studies, these include: “cephalosporin”, “ceftriaxone”, “cefepime”, “cefuroxime”, “penicillin”, “amoxicillin”, and “Amoxiclav”.

### Study selection

Articles that were identified using the titles and abstracts ( $n=40$ ) were then screened for the eligibility against the inclusion criteria checklist by both reviewers. At the end of the screening process, only full text articles were included ( $n=7$ ), and any disagreement in the selection by any of the authors was resolved by discussion. The detailed PRISMA diagram is provided in Figure 1.

### Data collection process

All the data from the selected articles were collected using a data extraction tool that was designed in accordance with the objective of this review. These data are illustrated in Table 2.

### Data items

The following data were extracted: article characteristics (author, year); study design; study sites (single or multiple); intervention arm; comparator arm; sample size in each arm; dosage regimens used; identified organisms; primary outcome; secondary outcome; and PSI scores.

### Quality assessment and risk of bias

The Scottish Intercollegiate Guidelines Network (SIGN) tool was used to evaluate the quality of the included studies. The tool consists of a checklist with two sections to

**Table 2.** Characteristics of the included studies.

Study	Study design	PSI Score	Arm 1 with Dose (n)	Arm 2 with Dose (n)	Culture type	Main outcome
Lin et al., 2007 <sup>19</sup>	Randomized open-label (single center)	Not mentioned	Amoxiclav + clarithromycin 500 mg/100 mg IV Q8h (n = 24)	Levofloxacin 500 mg IV Q24h (n = 26)	Sputum	Clarithromycin + BL regimen was as clinically effective as levofloxacin.
Garin et al., 2014 <sup>13</sup>	Open-label, noninferiority, randomized trial (multicenter)	III, IV	Cefuroxime 1.5 g IV Q8h or Amoxiclav 1.2 g IV Q6h + Clarithromycin 500 mg IV/PO Q12h (n = 289)	Cefuroxime 1.5 g IV Q8h or Amoxiclav 1.2 g IV Q6h (n = 291)	Blood, sputum, and pleural fluid	Beta-lactam monotherapy was not inferior to the combined therapy. Patients infected with atypical pathogens or with PSI category IV pneumonia had delayed clinical stability with monotherapy.
Dean et al., 2006 <sup>20</sup>	Randomized, prospective, open-label (multicenter)	I, II, III	Clarithromycin 400 mg IV/PO Q12h + Ceftriaxone 1 g IV Q24h (n = not specified)	Gatifloxacin 400 mg IV/PO Q24h (n = not specified)	Blood and sputum	Clarithromycin-based regimen was similar to gatifloxacin in clinical outcomes.
Tamm et al., 2007 <sup>23</sup>	Prospective, randomized, open-label (multicenter)	III, IV, V	Ceftriaxone 1-2 g/day IV + azithromycin 500 mg Q24h (n = 135)	Ceftriaxone 1-2 g/day IV + clarithromycin 500 mg Q12h IV (n = 143)	Blood	Ceftriaxone plus azithromycin may be a better treatment option in terms of reducing the duration of therapy and LOS because it is as effective as clarithromycin based regimen.
Zervos et al., 2004 <sup>21</sup>	Randomized, open-label (multicenter)	III, IV, V	Ceftriaxone 1 g Q24h IV + azithromycin 500 mg Q24h IV (n = 110)	Levofloxacin 500 mg IV Q24h (n = 102)	Blood and sputum	The combination of a third-generation cephalosporin and a macrolide is at least as efficacious as monotherapy with a fluoroquinolone with enhanced anti-pneumococcal activity for hospitalized patients with moderate to severe CAP.

(continued)

Table 2. Continued.

Study	Study design	PSI Score	Arm 1 with Dose (n)	Arm 2 with Dose (n)	Culture type	Main outcome
Frank et al., 2002 <sup>22</sup>	Open-label, randomized trial (multicenter)	Not mentioned	Ceftriaxone 1 g IV Q24h + azithromycin 500 mg IV Q24h (n = 121)	Levofloxacin 500 mg IV Q24h (n = 115)	Blood and sputum	Levofloxacin monotherapy was at least as effective as a combination regimen of azithromycin and ceftriaxone in providing coverage against the current causative pathogens in CAP.
Rubio et al., 2008 <sup>24</sup>	Open-label, non-comparative (multicenter)	III and IV	Ceftriaxone 1 g/day IV + azithromycin 500 mg Q24h (n = 86)	Same patients switched to oral azithromycin only 500 mg (n = 86)	Blood and sputum	Combination treatment was effective and well tolerated in hospitalized patients with CAP.

PSI, Pneumonia Severity Index; IV, intravenous; PO, orally; CAP, community-acquired pneumonia; Q6h, every 6 hours; Q8h, every 8 hours; Q12h, every 12 hours; Q24h, every 24 hours; BL, beta-lactam; LOS, length of stay.

assess in the internal validity and provide an overall assessment of the included studies as high, medium, or low quality.

Data extraction was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) where the primary outcome from all the studies was the clinical success rate, which is defined as the time (in days) to reach the following criteria: 1) systolic blood pressure above 90 mmHg; 2) heart rate <100 beats per minute; 3) respiratory rate <22 breaths per minute; 4) temperature <38.3°C; and/or 5) oxygen saturation >90%.<sup>18</sup> Data on the causative organism and length of hospital stay were also collected.

## Results

### Study selection

Forty studies were identified from the primary and secondary search. Among them, six studies were duplicates and 17 studies had a design other than a randomized controlled trial (RCT). Finally, seven full text RCT studies were included.<sup>13,19–24</sup> Figure 1 summarizes the study selection process.

### Study characteristics

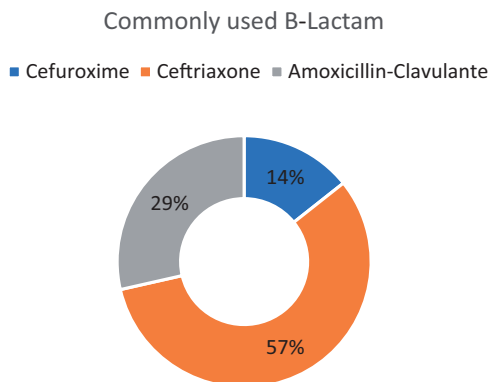
All of the included studies were conducted between 2002 and 2014. All of the studies were also multicenter trials except for Lin et al.<sup>19</sup> Three of the studies were from the USA,<sup>20–22</sup> and one each was from China,<sup>19</sup> Switzerland,<sup>13</sup> the Netherlands,<sup>23</sup> and Brazil.<sup>24</sup> The intervention arm in each study has a combination of a macrolide and a beta-lactam, while the comparator group was either a fluoroquinolone (n = 4) or another macrolide (n = 2), except if the study comparator was a control group. The length of hospital stay was reported in five studies,<sup>19–24</sup> and the clinical success rate was reported in all of the included studies.<sup>13,19–24</sup>

### Beta-lactam selection and use in combination therapy

In this systematic review, all of the seven included studies were published between 2002 and 2014, as shown in Table 2. Patients who were taking azithromycin received a dose of 500 mg per day. Those who received clarithromycin were administered a dose between 300 mg and 1000 mg per day. Similar doses of clarithromycin were administered using the oral route compared with the intravenous (IV) route, where the oral route was equivalent to the IV route for patients who were being treated for CAP.<sup>25</sup> Azithromycin was administered IV while clarithromycin was administered either orally or IV. The macrolide combination included either with a penicillin–lactamase inhibitor or a cephalosporin-based beta-lactam, and ceftriaxone was commonly used (Figure 2).

### Clinical success rate

The primary outcome was the clinical success rate among all the included trials. The clinical success rate was 87.55% after 10 or 14 days of therapy among the studies with data on azithromycin–beta-lactam and 75.42% after 5 or 7 days of therapy



**Figure 2.** Commonly used beta-lactams in combination with macrolides.

among the studies with data on clarithromycin–beta-lactam (Figure 3). Lin et al.<sup>9</sup> reported a success rate of 77% for clarithromycin, and Rubio et al.<sup>24</sup> reported a success rate of 95.5% for azithromycin.

The clinical success rate in the macrolide-based combination trials was defined as a clinical cure at the end of therapy, which is the resolution of signs and symptoms of pneumonia including dyspnea, cough, sputum, and fever. This success rate was reported mostly in patients with a PSI score of III or IV (Figure 4).

### Causative microorganism

Five<sup>20–24</sup> out of the seven studies investigated the causative organisms in all the treatment arms. Among all the isolated organisms, *S. pneumoniae* was commonly found in both of the macrolide groups, but more *S. pneumoniae* was found in the clarithromycin–beta-lactam-based group compared with the azithromycin group. An azithromycin–beta-lactam-based regimen had more isolates of *Hemophilus influenza* than in the clarithromycin–beta-lactam group. However, both regimens had the same killing effect on *Mycoplasma pneumoniae* (Figure 5).

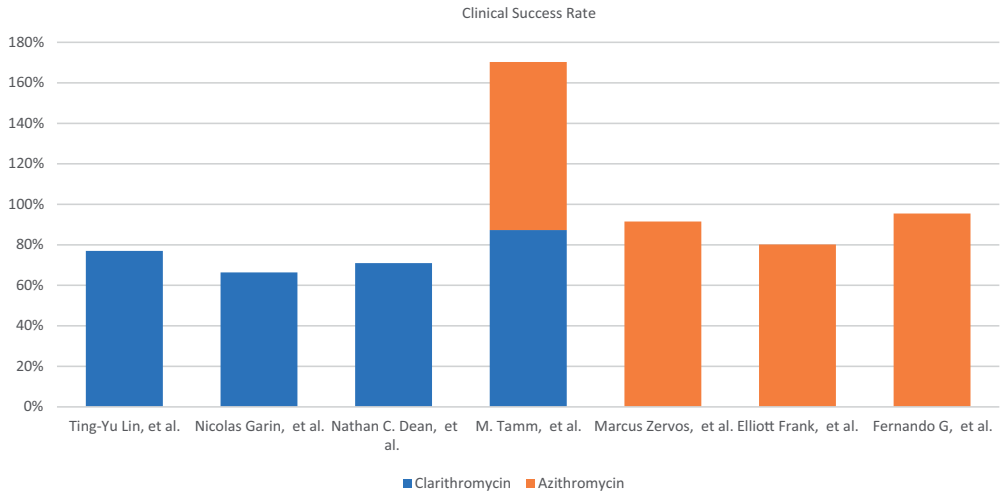
### Length of hospital stay

Data for the length of the hospital stay was retrieved from five clinical trials<sup>13,19,20,23,24</sup> (Figure 6). Patient who were treated with an azithromycin-based regimen spent more days in hospital than those treated with a clarithromycin-based regimen. The mean length of the hospital stay was 8.45 and 7.25 days, respectively.

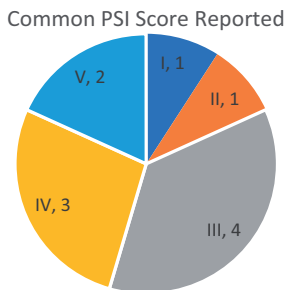
### Methodological quality and risk of bias within individual studies

The quality of the studies was assessed using the SIGN tool.<sup>26</sup> Seven full text RCT studies were included in this





**Figure 3.** Percentage of clinical success rate among both macrolide–beta-lactam-based regimens.



**Figure 4.** Common Pneumonia Severity Index (PSI) score reported.

study<sup>13,19–24</sup> on the basis of the SIGN tool’s assessment of quality. Five studies were of high quality<sup>13,19,20,22,24</sup> and two studies were of medium quality,<sup>21,23</sup> with no study in the low quality category. All the reviewers agreed to include these seven studies for further analysis. All the included studies included were open-label trials, and there was no blinded treatment allocation process. Participants in all of the studies were randomized to the treatment groups, except for one study, Rubio et al.,<sup>24</sup> because no comparator was used. Overall, the results of all the studies were directly

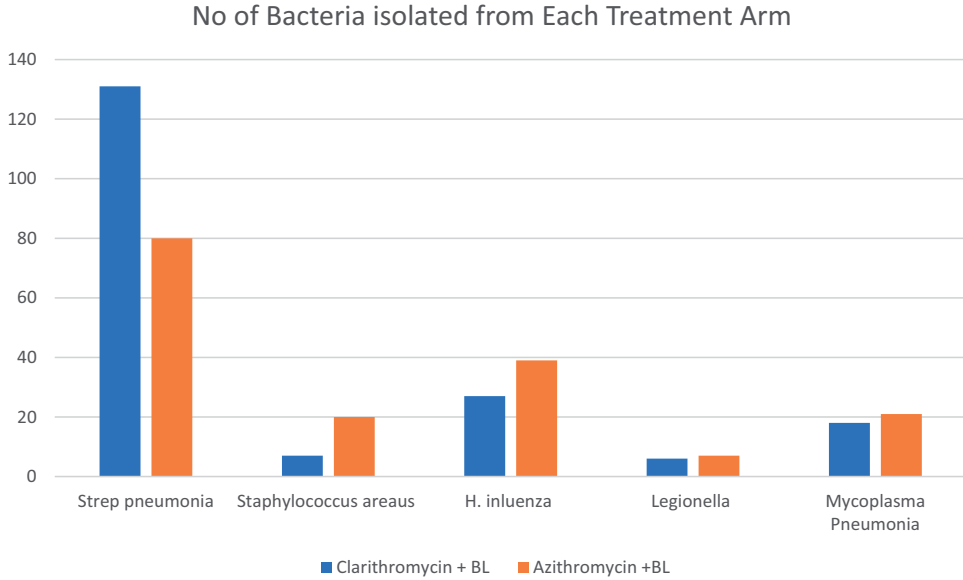
applicable to the patient group that was targeted in each study.

## Discussion

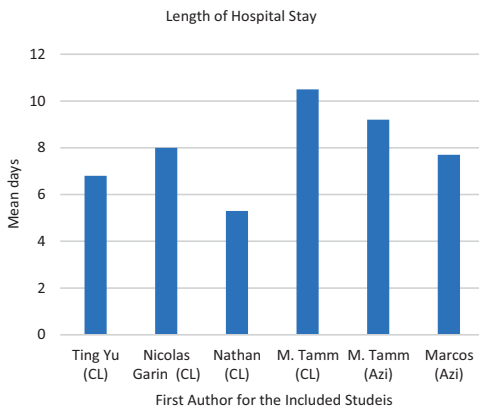
The 2019 IDSA guidelines recommend the combination of a beta-lactam and a macrolide to treat hospitalized patients with moderate to severe CAP.<sup>6</sup>

Both azithromycin–beta-lactam and clarithromycin–beta-lactam combinations have shown adequate efficacy in treating patients with CAP, with a higher clinical cure rate at the end of therapy using an azithromycin-based regimen. In our review, a clinical success rate of 87.55% after 10 or 14 days of treatment was reported for studies with an azithromycin–beta-lactam regimen, and a success rate of 75.42% after 5 or 7 days of treatment was reported among studies with a clarithromycin–beta-lactam regimen. In accordance with our study, a prospective study comparing clarithromycin–ceftriaxone (n = 106) and gatifloxacin (n = 99) showed a clinical success rate of 91% and 97%, respectively.<sup>27</sup> A multicenter study was performed to compare moxifloxacin monotherapy





**Figure 5.** Number of bacteria isolated from each treatment arm.



**Figure 6.** Length of hospital stay (mean number of days).

(n = 233) to clarithromycin–amoxicillin (n = 134), and that study showed a high clinical success rate of 93.6% and 93.7%, respectively, 7 to 10 days after the end of therapy. Most of the included patients who were in that study (84%) had class a PSI score of I, II, or III.<sup>28</sup> Both studies are consistent with this review, which emphasizes

the high clinical rate with a clarithromycin-based regimen. In our study, most patients with a high clinical success rate had a PSI score of III or IV (Figure 4). The high clinical success rate could reflect the need for a potent antimicrobial regimen in patients with a higher PSI score, where the combination of a macrolide and beta-lactam had lower 14 and 30-day mortality compared with fluoroquinolone monotherapy.<sup>14</sup> Moreover, macrolide combination therapy showed a significantly lower intensive care unit mortality rate (26.1%) in ventilated patients compared with the combination with fluoroquinolones (46.3%; hazard ratio 0.48, 95% confidence interval 0.23–0.97,  $p = 0.04$ ).<sup>8</sup> Another multicenter study with a randomized design compared moxifloxacin monotherapy with ceftriaxone with or without azithromycin, and that study showed a similar clinical success rate between both groups (83.3% in the moxifloxacin group [n = 108]; 79.6% in the comparator group [n = 113]), and in the latter

group, 70% of the patients received ceftriaxone combined with azithromycin.<sup>29</sup>

Combination therapy using a beta-lactam with a macrolide has been retrospectively assessed in many studies that investigated the clinical outcomes and the impact on hospitalization. These studies reported positive clinical outcomes that favored the addition of a macrolide such as erythromycin, clarithromycin, or azithromycin in hospitalized adults, and it also reduced the number of hospitalization days.<sup>30–32</sup> A recent open-label randomized trial compared ceftriaxone to ampicillin–sulbactam when clarithromycin or erythromycin was added to either of the beta-lactams in patients with CAP. The results showed a significantly higher effectiveness rate at day 7 in the ampicillin–sulbactam group ( $p=0.047$ ) compared with the ceftriaxone group in the validated per-protocol population.<sup>33</sup>

Multiple factors supported the superiority of combination therapy. For example, combination therapy can include two mechanisms of action so that the medications work at different sites of bacterial action, such as a beta-lactam that inhibits cell wall synthesis and a macrolide that inhibits protein synthesis. Moreover, macrolides reduce the adherence of *S. pneumoniae* to respiratory epithelial cells and show anti-inflammatory action by reducing the release of interleukin-8 and tumor necrosis factor- $\alpha$ .<sup>34,35</sup>

Adding a macrolide to a beta-lactam as empirical therapy was shown to reduce mortality in patients with pneumococcal pneumonia.<sup>36</sup> In our review, *S. pneumoniae* was commonly found in both macrolide groups, with 130 isolates in clarithromycin-based combinations and 80 isolates in the azithromycin-based group; additionally, 18 and 20 isolates from each group, respectively, were the atypical *M. pneumoniae*. In an open-label, prospective, nonrandomized study, patients

received sequential intravenous ceftriaxone and oral amoxicillin–clavulanate with or without a macrolide, where the macrolide selection was either clarithromycin ( $n=220$ ) or azithromycin ( $n=383$ ). *S. pneumoniae* was the most frequently isolated organism among all the isolates with 27 and 35 patients, respectively, and *M. pneumoniae* was isolated from six and ten patients from each group, respectively.<sup>37</sup> Higher *S. pneumoniae* eradication rates with clarithromycin could be explained by the extent of antimicrobial activity. In *in vitro* studies, clarithromycin tended to have a lower minimum inhibitory concentration (MIC) compared with azithromycin for *S. pneumoniae* (0.015–16 mg/dL vs. 0.12–4 mg/dL). However, azithromycin had a lower MIC for *H. influenzae* (0.5–4 mg/dL vs. 8–16 mg/dL) and the atypical *M. pneumoniae* (0.00024–<0.01 mg/dL vs. 0.008–0.5 mg/dL) compared with clarithromycin.<sup>38</sup>

The length of the hospital stay was one of the most common outcomes that was investigated in five studies.<sup>19–23</sup> The average length for the hospital stay was 8.45 days in patients receiving beta-lactams in combination with azithromycin and 7.25 days for patients receiving beta-lactams in combination with clarithromycin. Compared with our findings, an open-label nonrandomized study by Sanchez et al.<sup>37</sup> showed that the mean length of the hospital stay was 7.4 days for an azithromycin-based regimen and 9.8 days for a clarithromycin-based regimen. In another study with a prospective observational design that compared clarithromycin with ceftriaxone ( $n=209$ ) to levofloxacin ( $n=250$ ), the length of the hospital stay was 6 and 5 days, respectively.<sup>39</sup> When the azithromycin–beta-lactam combination was compared with beta-lactam monotherapy in an observational study by Ito et al.,<sup>40</sup> fewer hospitalization days (10 days) were found with the azithromycin–beta-lactam combination compared

with monotherapy (12 days), but this difference was not statistically significant. Several factors could play a role in the hospitalization days including the patient's condition, illness severity using the PSI score, patient characteristics, and initial antibiotic treatment. Menendez et al.<sup>41</sup> reported a hospital stay of 8 days in patients who received macrolide monotherapy, 8 days in patients who received third-generation cephalosporin combined with a macrolide, and 6 days in patients receiving amoxicillin–clavulanic acid and a macrolide compared with the initial antibiotic treatment. Thus, a shorter length of hospital stay is shown by patients who receive a macrolide–beta-lactam combination, but clarithromycin was not superior to azithromycin.

For the pharmacokinetic profiles, azithromycin has a lower incidence of drug–drug interactions compared with clarithromycin, which might influence the clinical decision when selecting the macrolide that is to be combined with a beta-lactam. For example, patients on theophylline, carbamazepine, or digoxin are at a high risk of reaching toxic levels when using clarithromycin because digoxin increases the plasma concentration of clarithromycin and azithromycin, whereas none of these interactions have been reported for azithromycin.<sup>42</sup> Additionally, a longer elimination half-life for azithromycin (68 hours) allowed for a single-dose daily regimen, while clarithromycin (half-life, 5–7 hours) is usually prescribed as a twice-daily regimen.<sup>43</sup>

## Conclusion

This systematic review and qualitative evidence synthesis reported inter-class macrolide differences. Both azithromycin and clarithromycin in combination with a beta-lactam have shown a significant clinical success rate at the end of therapy, with higher rates of a clinical cure at the end of therapy with an azithromycin-based

regimen. However, if a shorter hospital stay is the main focus during the management of patients with CAP, then a clarithromycin-based combination would be the therapy choice. The susceptibility data for the concerned facility must be considered when deciding upon the treatment selection.

## Clinical implications

- The clarithromycin–beta-lactam combination regimen was associated with a shorter hospital stay.
- Macrolides and azithromycin both have a relatively safe pharmacokinetic profile in terms of interactions.
- The selection of an intra-class macrolide combination with a beta-lactam depends on clinical prognosis and the patient's condition.
- Few clinical trials have investigated the safety and efficacy profile of intra-class macrolides with beta-lactam.

## Authorship statement

All the authors contributed equally to this research manuscript. The final manuscript has been read by all the authors, and all authors agreed to submit it for publication.

## Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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