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Comparison of Effectiveness and Safety Between Ceftriaxone/azithromycin and Levofloxacin in Hospitalized CAP Patients: A Review

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ABSTRACT

Community-acquired pneumonia (CAP) is a major health issue as it is a highly prevalent disease with significant morbidity and mortality worldwide. Current guidelines recommend ceftriaxone/azithromycin combination or levofloxacin monotheraphy as one of the empirical antibiotic options in non-ICU hospitalized CAP patients. This literature review aims to evaluate the comparative effectiveness and safety of ceftriaxone/azithromycin combination therapy and levofloxacin monotherapy in non-ICU hospitalized CAP patients. Four databases (PubMed, Scopus, DOAJ, and Cochrane Library) were used for article search with Boolean approach. Five articles which met the inclusion and exclusion criteria were evaluated. Two RCTs compared the effectiveness and safety of ceftriaxone/azithromycin combination and levofloxacin monotherapy, while the other 3 studies did not compare the safety of both antibiotic regimens due to the limitations of retrospective study design. Five articles analyzed the effectiveness of both regimens on various outcomes such as clinical improvement, mortality, and length of stay. The results demonstrated that levofloxacin monotherapy had better clinical improvement, lower mortality, and reduced length of stay in non-ICU hospitalized CAP patients compared to ceftriaxone/azithromycin combination. However, the safety of both treatment regimens is still uncertain due to the limited number of studies evaluating the incidence of adverse events.
Keywords: CAP; effectiveness; safety; ceftriaxone/azithromycin; levofloxacin

INTRODUCTION

Community-acquired Pneumonia (CAP) is a common lower respiratory tract infection in the community. Pneumonia affects about 450 million people every year. The incidence of CAP increases with age (Cillóniz et al., 2018). CAP causes 2.5 million deaths each year worldwide (World Health Organization, 2020). In Indonesia, there are 988 cases of CAP per 100,000 hospitalized cases with a case fatality rate (CFR) of 1.8% and greater than in the Philippines (Azmi et al., 2016).

CAP can be caused by various microorganisms, especially bacteria. Streptococcus *pneumoniae* is the most common typical bacterial pathogen causing CAP, representing 75% of all cases. Atypical pathogens such as *Mycoplasma*, *Legionella*, and *Chlamydia pneumoniae* are other bacteria that also frequently cause CAP, especially in the Asia-Pacific region (Metlay et al., 2019; Song et al., 2016).

However, the cause of pneumonia can be challenging to identify and sometimes it takes time for the results to be confirmed, whereas if pneumonia not treated immediately, it can lead to mortality. Therefore, selecting the right empirical antibiotic is a big challenge. A study in Spain reported that failure of empirical antibiotic treatment can increase mortality 11 times (Menéndez, Torres, Zalacaín, et al., 2004). Clinical failure occurred in approximately 15% of CAP patients on empiric antibiotics and led to prolonged length of stay in hospital, as well as increased treatment costs (Ott et al., 2012).

In adult patients with CAP in non-ICU hospitalized, current guideline suggest either combination of β-lactam and macrolide or respiratory fluoroquinolone monotherapy (Metlay et al., 2019). Both regimens are considered to have similar effectiveness (Liu et al., 2019). In terms of safety, meta-analyses published in 2018 and 2019 showed opposite results in both regimens (Liu et al., 2019; Zhang et al., 2018).

The increasing macrolides resistance in *S. pneumoniae* and *M. pnuemoniae* is an important issue to concern nowadays. In Asia, the prevalence of azithromycin resistance to *S. pneumoniae* was

69.7%, while resistance to *M. pneumoniae* was 63% and greater than in Europe and America (Kim et al., 2012; Wang et al., 2022). The high prevalence of macrolide resistance is caused by the extensive use of macrolides in clinical practice. Considering the existing macrolide resistance epidemiology, the use of respiratory fluoroquinolone may be an appropriate choice in the management of CAP.

In Indonesia, ceftriaxone and levofloxacin are the most widely consumed antibiotics for adult inpatients, and the highest consumption in the last 5 years (Limato et al., 2022). Until now, specific evaluations regarding the comparative effectiveness and safety of the combination of ceftriaxone/azithromycin and levofloxacin montherapy has not been sufficient. It is due to the limited number of studies that specifically compare the two antibiotic regimens. Therefore, this literature review was performed to compare the effectiveness and safety of the combination of ceftriaxone/azithromycin and levofloxacin monotherapy in non-ICU hospitalized CAP patients based on the latest available literature.

METHODS

Four databases (PubMed, Scopus, DOAJ, and Cochrane Library) were searched for literature published in 2013-2023. The following Boolean search strategy was applied: (pneumonia OR community-acquired pneumonia OR CAP) AND (fluoroquinolone OR levofloxacin) AND (β-lactam OR beta-lactam OR ceftriaxone) AND (macrolide OR azithromycin). The inclusion criteria used were 1) studies containing the effectiveness and safety between ceftriaxone/azithromycin combination and levofloxacin monotherapy in non-ICU hospitalized CAP patients; 2) randomized controlled trial (RCT) and observational study designs; 3) English language articles. Exclusion criteria used were 1) pediatric, cancer, pregnant, and breastfeeding patients; 2) articles not full text; 3) paid articles. A total of 253 articles were obtained and screened. After further screening, only 5 articles met the inclusion and exclusion criteria. The detailed selection process can be seen in Figure I.

RESULTS

Among the 253 articles obtained from the database, five articles which met the inclusion and exclusion criteria were further evaluated in this literature review. All subjects in the included studies were adult patients with CAP. The characteristics of each article are presented in Table I, while the summary of findings are presented in Table II.

Effective initial antibiotic use is critical in the management of CAP, as delayed and inappropriate treatment can lead to adverse outcomes such as increased risk of complications, length of hospitalization, mortality and antibiotic resistance (Bell et al., 2014; Dinh et al., 2021; Phua et al., 2010). Recent guidelines recommend a combination of ceftriaxone/azithromycin or levofloxacin monotherapy as a therapeutic regimen for hospitalized CAP patients, especially non-ICU patients (Metlay et al., 2019).

Ceftriaxone is a broad spectrum β-lactam antibiotic with broader coverage of gram-negative bacteria than previous generation cephalosporins. The addition of macrolides to β-lactams has the benefit of improving coverage of atypical pathogens better than β-lactam monotherapy. Reports on the prevalence of atypical pathogens vary widely from 5% to more than 28% in hospitalized CAP patients (Arnold et al., 2007; Gramegna et al., 2018). Ceftriaxone/azithromycin combination regimens work in two different ways, thus providing a synergistic effect on CAP therapy. Ceftriaxone works by inhibiting cell wall synthesis and azithromycin inhibits bacterial protein synthesis. In addition, azithromycin is known to have immunomodulatory effects, which may moderate the inflammatory response independently of antibacterial activity (Kovaleva et al., 2012).

Levofloxacin has broad spectrum bactericidal activity including both typical and atypical pathogens causing CAP, so it is referred to as a respiratory fluoroquinolone. Levofloxacin works by inhibiting bacterial DNA synthesis. In addition, the concentration of levofloxacin in the lung was about 2-5 times higher than its plasma concentration. The Gotfried et al. (2001) study showed that the plasma concentration of 750 mg levofloxacin were 12.0±3.0 μg/mL with alveolar epithelial lining fluid concentration of 22.1±14.9 μg/mL 4 hours after administration.

In this literature review, we included 5 studies that compared the effectiveness of ceftriaxone/azithromycin combination and levofloxacin monotherapy with various outcomes, such as clinical improvement, mortality, and length of stay (LOS). All studies were conducted on adult

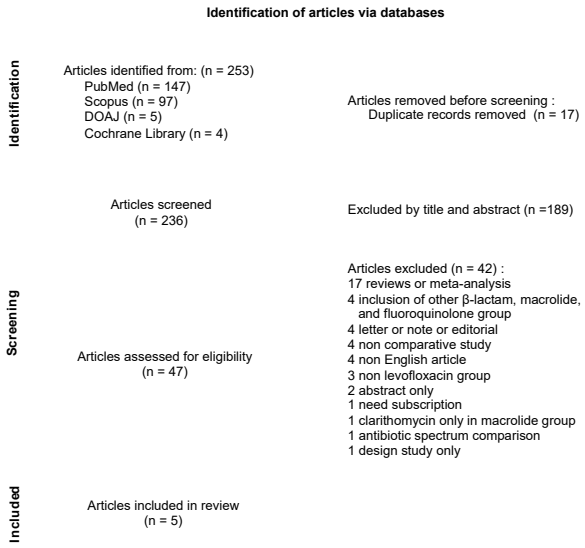

Figure I. Article selection flowchart

subjects with CAP. Of the 5 studies, 2 RCTs compared the efficacy and safety of ceftriaxone/azithromycin combination and levofloxacin monotherapy, while the other 3 studies did not compare the safety of both antibiotic regimens due to the limitations of retrospective study design.

Clinical Improvement

Clinical improvement in CAP patients can be evaluated by improvement in vital signs (body temperature, respiratory rate, heart rate, and O_2 saturation), improvement in cough symptoms, and absence of sputum production. Randomized controlled trial by Yadegarynia et al. (2022) reported levofloxacin monotherapy was significantly more effective than ceftriaxone/azithromycin combination. Respiratory rate on day 3 (21.14 ± 3.95 vs 22.84 ± 4.12; p 0.001), O_2 saturation on day 3 (90 ± 4.25 vs 88 ± 3.96; p < 0.001), and O2 saturation on day 5 (93 ± 4.12 vs 92 ± 3.80; p 0.006) of antibiotic administration were better in the levofloxacin monotherapy group. The absence of sputum and improvement of cough symptoms on days 3 and 5 after antibiotic administration were also significantly better in the levofloxacin group than the ceftriaxone/azithromycin combination (p < 0.01) (Yadegarynia et al., 2022).

Another RCT by Izadi et al. (2018) and a cohort study by Suratini et al. (2017) reported that levofloxacin monotherapy was as effective as ceftriaxone/azithromycin combination. The study by Farida et al. (2022) reported higher clinical improvement in the levofloxacin monotherapy group compared to the ceftriaxone/azithromycin combination group. Only 1 out of 30 patients showed no clinical improvement after 3 days of antibiotic administration (Farida et al., 2022). This result contradicts the study by Uryasev et al. (2021) who reported the effective respone of the ceftriaxone/azithromycin combination was higher than levofloxacin monotherapy by 47% and 38%, respectively. However, levofloxacin monotherapy reduced the risk of antibiotic replacement by 14%, while the ceftriaxone/azithromycin combination increased the risk of antibiotic replacement by 11% (Uryasev et al., 2021).

The rate of clinical improvement in CAP patients was influenced by several factors such as age, gender, number of comorbidities, number of signs and symptoms at admission, hypoxemia, and severity of pneumonia. Younger age, female, absence of dyspnea and confusion on admission, mild severity of pneumonia, no comorbid chronic bronchitis, no pleural effusion, no multilobar CAP, and no cardiac and respiratory complications were predictors of early clinical stability (≤ 3 days) (Garin et al., 2016; Menéndez, Torres, Rodríguez de Castro, et al., 2004).

Table I. Characteristics of the included studies

Author	Title	Design and Location	Number Participants (n)	Outcome Measured
Suratini et al. (2017)	Cost-Effectiveness Analysis of Ceftriaxone-Azithromycin Combination and Single Levofloxacin as Empirical Antibiotics in Community-Acquired Pneumonia Inpatients at Persahabatan Hospital	Design: Retrospective Cohort Location: Persahabatan hospital, Jakarta, Indonesia	CFX+AZH = 64 LFX = 36	1. Success rate (the patient was cured or showed clinical improvement) 2. Mortality 3. LOS
Izadi et al. (2018)	Levofloxacin Versus Ceftriaxone and Azithromycin Combination in the Treatment of Community Acquired Pneumonia in Hospitalized Patients	Design: Randomized open label Location: Qaem hospital, Karaj, Iran	CFX+AZH = 75 LFX = 75	1. Clinical improvement 2. Mortality 3. LOS 4. Adverse event
Uryasev et al. (2021)	Effectiveness of antimicrobial therapy for community-acquired pneumonia in real clinical practice	Design: Retrospective observational Location: Regional Clinical Hospital Ryazan, Russia	CFX+AZH = 19 LFX = 37	Effective respone (no need to replacement of antibiotic)
Farida et al. (2022)	Cost-effectiveness analysis of empiric antibiotics in hospitalized community-acquired Pneumonia	Design: Retrospective observational Location: University Hospital in Surakarta, Central Java, Indonesia	CFX+AZH = 13 LFX = 30	Clinical improvement after 72 hours of antibiotic therapy
Yadegarynia et al. (2022)	Levofloxacin versus ceftriaxone and azithromycin for treating community-acquired pneumonia: a randomized clinical trial study	Design: Randomized controlled trial Location: Labbafinejad hospital, Tehran, Iran	CFX+AZH = 77 LFX = 74	1. Clinical improvement 2. LOS 3. Adverse event

Mortality

There were 2 studies that analyzed mortality as one of the outcomes, RCT by Izadi et al. (2018) reported no deaths in both groups of antibiotic regimens. The cohort study reported mortality in the combination of ceftriaxone/azithromycin group as many as 3 patients (4.7%), while in the levofloxacin group as many as 1 patient (2.8%) (Suratini et al., 2017).

Mortality rates in CAP patients have been reported in several studies. Garcia-Vidal et al. (2008) reported factors such as age ≥ 70 years, shock at admission, altered mental status, and inappropriate empirical antibiotic therapy were associated with early death (<48 hours) in elderly patients. Acute respiratory distress, sepsis shock, and congestive heart failure (CHF) or arrhythmia were the main causes of death in the study (Garcia-Vidal et al., 2008). In addition, a study conducted in Indonesia

Table II. Summary of findings regarding the efficacy and safety of combination ceftriaxone/azithromycin and levofloxacin monotheraphy in CAP patients

Author	Antibiotic Regimen		Efficacy Results	Safety Results
	Combination	Monotherapy		
Suratini et al. (2017)	IV CFX 2g or 3g once daily + PO AZH 500 mg once daily	IV LFX 750 mg once daily	1. The success rates in the CFX+AZH and LFX groups were not significantly different (61 patients (95.3%) vs 35 patients (97.2%); p 1.000). 2. Three patients (4.7%) died in the CFX+AZH group and 1 patient (2.8%) died in the LFX group. 3. Median LOS in both groups was significantly different at 7 vs 6 days (p 0.004), respectively.	not studied
Izadi et al. (2018)	IV CFX 1g twice daily + PO AZH 250 mg once daily for 7-10 days	PO LFX 750 mg once daily for 5 days	1. There was no significant difference in body temperature (p 0.09), WBC count (p 0.15), and respiratory sound (p 0.18). 2. There were no reported in-hospital deaths in either group. 3. The average LOS was not significantly different in the LFX and CFX+AZH groups (3.3 vs. 3.4 days; p 0.15).	Two patients (2.7%) experienced skin rashes in the CFX+AZH group. Six patients (8%) experienced adverse events in the LFX group including skin rash (1 patient (1.3%)), GI problems (2 patients (2.7%)), and CNS complications (3 patients (4%)).
Uryasev et al. (2021)	CFX+AZH	LFX	The CFX+AZH group had better effective respon with no antibiotic replacement than the LFX group (9 (47%) vs 14 (38%)).	not studied
Farida et al. (2022)	CFX+AZH	LFX	Patients in the LFX group showed better clinical improvement than those in the CFX+AZH group (29 (97%) vs 9 (69%)).	not studied

Table II. Summary of findings regarding the efficacy and safety of combination ceftriaxone/azithromycin and levofloxacin monotheraphy in CAP patients

Author	Antibiotic Regimen		Efficacy Results	Safety Results
	Combination	Monotherapy		
Yadegarynia et al. (2022)	IV CFX 1g once daily + PO AZH 500 mg once daily for 5-7 days	PO LFX 750 mg once daily for 5 days	1. Clinical improvement in the LFX group was significantly better than the CFX+AZH group. 2. The LFX group had a shorter average LOS compared to the CFX+AZH group (5.14 days vs 6.72 days, p < 0.001).	The adverse events were not statistically different between the two groups (p 0.885). A total of 10 patients (12.95) in the CFX+AZH group and 11 patients (14.8%) in the LFX group experienced adverse events including nausea (3 (3.8%) vs 5 (6.7%)), rash (6 (7.7%) vs 5 (6.7%)), headache (0 vs 1 (1.3%)), and other (1 (1.2%) vs 0).

Abbreviation: CFX+AZH, ceftriaxone+azithromycin; LFX, Levofloxacin; IV, intravenous; PO, per oral; LOS, length of stay; CNS, central nervous system; WBC, white blood cell; GI, gastrointestinal.

more than 5 and low albumin level (<3 g/dL) were also predictors of mortality (Firmansyah et al., 2015).

Length Of Stay (LOS)

There were 3 studies that analyzed length of stay as one of the outcomes, 2 of which reported significantly different LOS. RCT by Yadegarynia et al. (2022) reported a lower median LOS in the levofloxacin monotherapy group compared to the ceftriaxone/azithromycin combination group (5.14 ± 2.67 vs 5.14 ± 2.67 (p < 0.001)). Similar finding were also found in the cohort study by Suratini et al. (2017), where the median length of stay for levofloxacin monotherapy group was lower (6 days (2-11) vs 7 days (3-14) (p 0.004)). Another RCT reported there was no significant difference in LOS between both antibiotic regimen groups (p 0.15) (Izadi et al., 2018).

The length of stay in hospital was related to the rate of clinical stability achieved by CAP patients after antibiotic administration. Available study showed patients who achieved clinical stability ≤ 3 days had significantly lower LOS (6 days (IQR 4-10)) than patients who did not achieve clinical stability (10 days (IQR 7-15)) (p < 0.001) (Garin et al., 2016). It can be concluded that LOS in patients receiving levofloxacin monotherapy was lower because the regimen had a better clinical improvement rate than the ceftriaxone/azithromycin combination.

Safety

There are 2 studies that analyzed the incidence of adverse events in evaluating the safety of both antibiotic regimens in hospitalized CAP patients. The results of RCTs by Izadi et al. (2018) and Yadegarynia et al. (2022) showed levofloxacin monotherapy caused more adverse events than ceftriaxone/azithromycin combination. However, the results showed not significantly different (p 0.085) (Yadegarynia et al., 2022).

Common adverse events in ceftriaxone/azithromycin combination are skin rash and nausea, while in levofloxacin monotherapy are rash, gastrointestinal disorders (nausea, vomiting, diarrhea), and central nervous system (dizziness and headache). The mechanism of levofloxacin that may be involved with central nervous system adverse events is its ability as an inhibitor of gamma-aminobutyric acid (GABA) receptors and N-methyl-D-aspartate (NMDA) receptors (Moorthy et al., 2008). Inhibition of GABA receptors also has the potential to affect the function of the vagus nerve, which controls the gastrointestinal tract (Cannizzaro et al., 2021). Based on the findings, it can be stated that the incidence of adverse events was less in CAP patients who received the ceftriaxone/azithromycin combination. This finding is in line with a 2018 meta-analysis which stated that the side effects of ceftriaxone and macrolide combination were significantly lower than fluoroquinolone monotherapy (Zhang et al., 2018).

There were no reports of cardiovascular events in the 2 RCTs. Cardiovascular events need to be cautioned in the treatment of macrolides and fluoroquinolone. Macrolides may prolong the QT interval and cause arrhythmias due to effects on potassium ion channels. Especially, erythromycin use in CAP patients was associated with a 68% higher risk of hospitalized cardiac events (heart failure and arrhythmias). A total of 6 out of 207 patients (2.9%) (HR 0.70; 95% CI 0.39 - 1.26) who received azithromycin and 3 out of 194 patients (1.5%) (HR 0.50; 95% CI 0.15 - 1.64) who received levofloxacin experienced arrhythmia, so it can be said that the risk of arrhythmia was lower in CAP patients who received levofloxacin (Postma et al., 2019).

The strength of this literature review was the use of a search strategy to identify relevant literature on the effectiveness and safety of ceftriaxone/azithromycin combination and levofloxacin monotherapy in non-ICU hospitalized CAP patients. This allowed us to identify studies that did not mention both antibiotic regimens in the abstract, but included data regarding both regimens in the publication and supplementary data. We also identified 2 recent RCTs that had not previously been included in available meta-analyses (Liu et al., 2019; Zhang et al., 2018). However, this literature review also had limitations such as observational studies were included in the review, so the safety outcomes were unknown in these studies.

Future studies need to compare the effectiveness and safety of ceftriaxone/azithromycin combination and levofloxacin monotherapy in hospitalized CAP with RCT design. Considering the increased prevalence of CAP and the cause of numerous deaths worldwide, as well as the impact on the economic burden.

CONCLUSION

The results of this literature review demonstrated that levofloxacin monotherapy had better clinical improvement, lower mortality, and reduced length of stay in non-ICU hospitalized CAP patients compared to ceftriaxone/azithromycin combination. However, the safety of both treatment regimens remains uncertain due to the limited number of studies evaluating the incidence of adverse events. Further comparative safety studies are needed regarding ceftriaxone/azithromycin combination and levofloxacin monotherapy in CAP.

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