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Effectiveness of β-lactam and Macrolide Antibiotic Combination in Patients with Community-Acquired Pneumonia: A Review

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Abstract: Community-acquired pneumonia (CAP) is a clinically significant lung infection and a leading cause of infectious disease-related death, especially in patients with high-risk factors. This study aims to analyze the effectiveness of a combination of β-lactam and macrolide antibiotics in the treatment of CAP and its impact on reducing mortality. Using the Systematic Literature Review method from sources such as Google Scholar, PubMed, and ScienceDirect, 10 national and international journals were reviewed to evaluate the effectiveness of this combination compared to monotherapy and other combination options. Results showed that the combination of β-lactams and macrolides is effective in improving clinical outcomes, accelerating recovery, and reducing mortality in CAP patients, especially against atypical pathogens that are often not fully treated with β-lactam monotherapy. Factors such as seasonal variations and the patient's state of health also influence the response to this therapy. The most commonly used antibiotics in this combination are Ceftriaxone or Ampicillin/Sulbactam as β-lactams, paired with Azithromycin or Clarithromycin as macrolides. Therefore, the combination of β-lactams and macrolides is considered an effective primary therapy option for CAP, in accordance with the national guidelines for medical services in Indonesia, which allows flexibility in treatment according to the clinical condition of the patient and the characteristics of the pathogen present.

Keywords: Antibiotics; CAP; Community Pneumonia; β-lactams; Macrolides.

Introduction

Pneumonia is an inflammation of the lung parenchyma, including the alveoli, bronchi, or bronchioles, leading to lung consolidation and impaired oxygen exchange. In healthy individuals, the alveoli are filled with air, whereas in pneumonia patients, the alveoli are filled with pus and fluid, making breathing difficult [1]. Symptoms of pneumonia include productive cough, fever, chills, and headache. This disease can be caused by bacteria, viruses, or fungi and spreads through coughing and sneezing. Epidemiologically and clinically, pneumonia is divided into four types: community-acquired pneumonia (CAP), nosocomial pneumonia (hospital-acquired pneumonia), aspiration pneumonia, and pneumonia in immunocompromised patients. Pneumonia is one of the most significant Acute Respiratory Infections (ARI), as it is a leading cause of death, particularly in children worldwide, including in Indonesia [2].

Community-acquired pneumonia is an acute inflammation of the lung parenchyma caused by pathogens acquired outside the hospital or community [3]. This type of pneumonia requires antibiotic treatment as part of its therapy. The most common cause of CAP is Streptococcus pneumoniae, although other pathogens such as Haemophilus influenzae, viruses, and fungi may also be involved [4]. Symptoms of CAP are similar to those of other types of pneumonia, with characteristics such as productive cough, fever, chest pain, and shortness of breath. This disease is more commonly experienced by individuals with risk factors such as advanced age, chronic diseases, or weakened immune systems [5]. The World Health Organization (WHO) reports that community-acquired pneumonia (CAP) causes nearly 3 million deaths annually. The mortality rate is higher in hospitalized CAP patients, ranging from 6% to 20%, depending on the severity of the disease and the available healthcare facilities. The high antimicrobial resistance rate of Streptococcus pneumoniae exacerbates the situation, increasing the number of CAP patients requiring hospitalization and making the treatment of this infection more complicated [6]. Proper antibiotic use is crucial to prevent resistance. The high prevalence of pneumonia, antibiotic use, and global resistance events drives further research on antibiotic use profiles in community pneumonia patients. Rational antibiotic therapy can reduce the prevalence of pneumonia and achieve therapeutic goals [7].

Antibiotic therapy is the primary approach in managing bacterial infections in pneumonia. However, several studies have shown that monotherapy is often insufficient in managing severe pneumonia cases. One of the main reasons is the diversity of microorganisms involved, such as Streptococcus pneumoniae and Haemophilus influenzae, which have varying resistance mechanisms against specific antibiotics. Additionally, pneumonia-causing bacteria can form biofilms, which reduce the effectiveness of antibiotics and allow them to persist in the body despite treatment [8]. The administration of combination antibiotics can broaden the spectrum of antibiotic activity, which is expected to provide beneficial synergistic effects [9]. Clinical studies

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indicate that combination therapy, especially with broad-spectrum antibiotics, can be more effective in reducing mortality risk compared to monotherapy, especially in patients with severe pneumonia requiring hospitalization. The use of a combination of beta-lactams and macrolides has been found to be more effective in suppressing the development of antibiotic resistance and accelerating patient recovery compared to monotherapy [10].

This study aims to evaluate the effectiveness of the combination of beta-lactam and macrolide antibiotics in the treatment of community-acquired pneumonia (CAP). The primary focus is to determine how this combination can reduce mortality rates in patients with CAP, especially those at high risk or requiring intensive care in the ICU.

Research Methods

The method used in this study is a Systematic Literature Review, employing a comprehensive and descriptive approach through literature search in research journal databases. The research materials for this study were obtained from Google Scholar, PubMed, and ScienceDirect. The keywords used for the literature search in this study were "Pneumonia, Bacterial" OR "Community-Acquired Infections" AND ("Antibiotics" OR "β-Lactams" OR "Macrolides") AND "Treatment Outcome" AND "Humans."

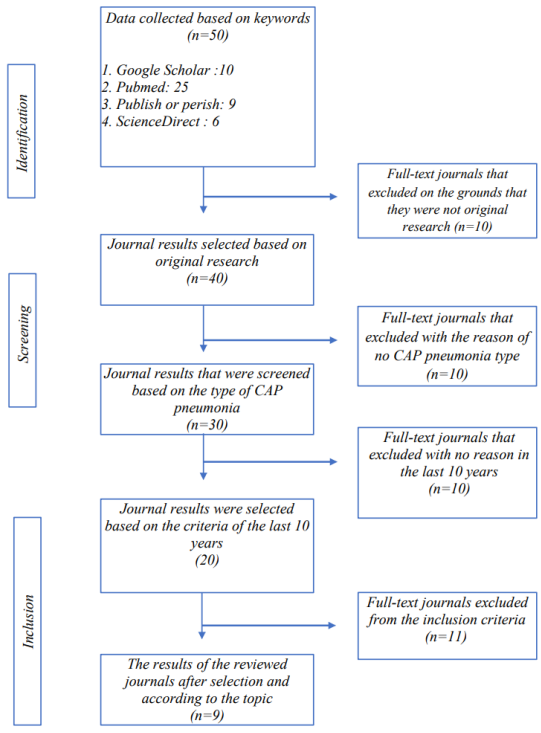

Figure 1. Flow Chart of the Systematic Literature Review

The Systematic Literature Review approach applied supports the PICO analysis by selecting literature from scientific databases to ensure comprehensive coverage of the effectiveness of antibiotics in CAP patients. The literature search with relevant keywords ensured a focus on antibiotic effectiveness without directly comparing it to other therapies, as well as assessing its impact on symptom recovery and mortality reduction in patients.

Table 1. PICO Framework

PICO Analysis	Results
Population	Patients with Community-Acquired Pneumonia (CAP).
Intervention	Use of a β-Lactam and Macrolide antibiotic combination.
Comparison	No comparison made.
Outcome	Effectiveness of the β-Lactam and Macrolide antibiotic combination in reducing symptoms, accelerating recovery, and lowering mortality rates in CAP patients.

The researcher conducted the data collection process by first identifying 50 articles from various sources, including Google Scholar (10 articles), PubMed (25 articles), Publish or Perish (9 articles), and ScienceDirect (6 articles), which were selected based on specific keywords. From these, 10 articles were excluded because they were not original research, leaving 40 articles. Next, 10 more articles were eliminated because they did not discuss community-acquired pneumonia (CAP), resulting in 30 articles. The selection continued based on a 10-year time frame, and 10 more articles were removed because they did not meet the time criteria, leaving 20 articles. Finally, the selection process based on inclusion criteria resulted in 9 articles that were chosen for further review and were relevant to the topic.

Results and Discussion

In this study, 9 journals were included that discuss the combination of β-lactam antibiotics and macrolides in patients with Community-Acquired Pneumonia (CAP) from various countries, including South Korea, Japan, the United States, China, and Spain. Based on the studies reviewed, the combination therapy of β-lactam and macrolides consistently showed improved effectiveness in the treatment of community-acquired pneumonia (CAP) compared to monotherapy or alternative combinations. Several studies indicate that the use of β-lactam and macrolide antibiotic combinations for community-acquired pneumonia (CAP) patients consistently provides significant clinical benefits. However, variations in effectiveness remain, depending on factors such as seasonality, patient health conditions, pathogen types, and the personalized data-driven approach used. The effectiveness of the β-lactam and macrolide combination therapy between autumn and spring. Improved clinical responses in autumn may be due to the seasonal fluctuations in pathogen types. In autumn, certain pathogens may be more sensitive to this combination therapy, while in spring, the presence of other pathogens less responsive to this combination may increase. This suggests that antibiotic responses are not only influenced by the type of antibiotic used but also by the seasonal epidemiological factors related to pathogens. This study emphasizes the importance of considering seasonal aspects in selecting the appropriate antibiotic therapy to improve treatment effectiveness [11]. This finding is consistent with the results, which showed that the β-lactam and macrolide combination therapy significantly reduced mortality in ICU patients with CAP. These patients, particularly those

infected by atypical pathogens, often have a poor response to β-lactam monotherapy. Therefore, the inclusion of macrolides in the combination therapy allows for broader coverage, especially against pathogens with specific resistance [12]. This finding, which showed that this combination not only reduced mortality but also accelerated recovery in patients with more severe conditions. The consistency of these findings underscores that the β-lactam and macrolide combination strategy is crucial, especially for critically ill patients, providing better protection against pathogens that are difficult to treat with single therapy [13][14].

Table 2. The Paper selection

Paper	Antibiotics	Effectiveness	Impact
[16].	Ceftriaxone and Azithromycin	Reduces mortality in patients with specific microbial etiology and high inflammatory status	Personalized therapy approach improves outcomes according to patient conditions
[18].	Ceftriaxone and Azithromycin	Reduces 30-day readmission rates compared to fluoroquinolones	Reduces the risk of relapse and post-treatment complications
[12].	Ceftriaxone and Azithromycin	Reduces mortality in community-acquired pneumonia patients in the ICU	Shortens ICU stay and enhances patient recovery
[11].	Ceftriaxone and Azithromycin	Effective in improving clinical outcomes in autumn and spring	Clinical response improves with minimal seasonal differences
[15].	Penicillin and Clarithromycin or Ceftriaxone and Erythromycin	Improves clinical outcomes in specific subpopulations	Machine learning algorithms help identify patients suitable for combination therapy
[19].	β-Lactam + Macrolide	Superior in improving patient survival rates compared to fluoroquinolones	Enhances patient immune response to combination therapy
[14].	Penicillin and Azithromycin, Ampicillin and Clarithromycin	More effective in reducing mortality compared to monotherapy	Faster recovery compared to monotherapy
[21].	Ampicillin and Azithromycin	Reduces mortality in community-acquired pneumonia patients compared to monotherapy	Improved survival due to coverage of atypical pathogens
[13].	Ceftriaxone and Azithromycin	Provides better clinical outcomes compared to fluoroquinolones	Speeds up patient recovery and provides coverage against sensitive pathogens
[17].	Tazobactam and Azithromycin	Better than levofloxacin + β-lactam in reducing mortality	Synergistic effect of azithromycin accelerates healing and reduces inflammation

In terms of improving effectiveness through a personalized approach using machine learning to identify subpopulations of patients who may benefit most from the macrolide and β-lactam combination. This algorithm allows the prediction of specific factors influencing patient responses, such as pneumonia severity and underlying health status [15]. This approach aligns, which showed that patients with high inflammatory status gained greater benefit from this combination therapy. A personalized approach, there is an opportunity to optimize antibiotic therapy, considering not only the type of pathogen but also the individual patient's condition. Thus, this approach can maximize clinical benefits for the appropriate subpopulation while minimizing the risk of undesirable side effects. Moreover, many studies have compared the combination of β-lactam and macrolides with fluoroquinolones in empirical CAP therapy [16]. The combination of azithromycin and β-lactam performed better than the combination of levofloxacin and β-lactam, particularly due to the stronger anti-inflammatory effects of azithromycin [17]. Patients receiving the β-lactam and macrolide combination had a lower 30-day readmission rate compared to those receiving fluoroquinolones [18]. This combination is more effective in improving survival in severe CAP patients. These findings emphasize the importance of therapies that can enhance immune responses and provide an advantage against atypical pathogens that cannot be addressed with fluoroquinolones alone [19]. Other studies, the importance of the β-lactam and macrolide combination in addressing atypical pathogens that are often resistant to β-lactam antibiotics alone. Atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are generally not targeted by β-lactams but can be effectively treated with macrolides, which have antibacterial activity against these pathogens. Additionally, macrolides have immunomodulatory effects that help enhance the immune response to infections, accelerate healing, and reduce the risk of complications. This combination is particularly relevant in managing community-acquired pneumonia cases with diverse pathogen profiles, where monotherapy may not be sufficiently effective [13][19].

The series of findings suggests that the combination of β-lactam and macrolides not only expands therapeutic

coverage but also utilizes the immunomodulatory potential of macrolides, making it an important choice in the treatment of complex community-acquired pneumonia. The Minister of Health of the Republic of Indonesia's Decree Number HK.01.07/MENKES/2147/2023 regarding National Medical Service Guidelines for the Management of Pneumonia underscores the use of β-lactam and macrolide combinations as one of the primary treatment options for community-acquired pneumonia (CAP) patients, both in non-severe and severe cases [3]. This provision aligns with clinical evidence showing that this combination is effective, especially for high-risk patients or those requiring intensive care in ICUs. The guidelines support the flexibility of using combination antibiotics, particularly when treatment needs to be tailored to the patient's condition and pathogen potential. In severe pneumonia patients, the guidelines recommend the use of a β-lactam and macrolide combination or alternatives such as fluoroquinolones, which offer better therapeutic responses and broader pathogen coverage. This is consistent with data showing that the β-lactam and macrolide combination provides better effects against atypical pathogens, including when seasonal pathogen profiles affect treatment effectiveness.

The administration of β-lactam and macrolide is expected to improve patient outcomes for three reasons: the broader antibiotic spectrum due to the combination of two classes of antibiotics, the complementary mechanisms of action of macrolides and β-lactams, and the immunomodulatory capacity of macrolides [20]. With the available data, the combination of β-lactam and macrolide can be considered a first-line treatment for CAP, especially in patients with high-risk factors or those hospitalized in ICUs. This combination offers important therapeutic flexibility, allowing treatment approaches to be adapted to the patient's condition and the potential infections faced, while also accommodating seasonal variations in pathogen profiles [21].

The combination of β-lactam and macrolide in community-acquired pneumonia treatment, while effective in reducing mortality in certain populations, also presents various side effects that need attention. Cardiotoxic effects such as QT interval prolongation and the risk of dangerous arrhythmias [15][16]. The importance of close monitoring, especially in patients with cardiovascular comorbidities. The risk of drug interactions with statins and other medications metabolized by the same enzymes also underscores the need for careful evaluation of the patient's drug profile before prescribing this therapy [19][22].

Empirical antibiotics used in adult community pneumonia patients at X Surakarta Hospital had significant effectiveness in treating these lung infections [23]. This is in line with this study, which examined the effectiveness of beta-lactam antibiotics in elderly patients with community pneumonia, where the results showed that beta-lactams can provide a good response, even in older patient groups with higher comorbidities [24].

In addition, the study compared monotherapy and combination therapy in community pneumonia patients at a private hospital in Yogyakarta, and found that combination therapy provided better results in reducing mortality and complication rates [25]. This study is in line with the switch of intravenous to oral antibiotics on the length of hospitalization of community pneumonia patients, and found that the switch to oral therapy could reduce the duration of hospitalization, without compromising the effectiveness of therapy [26].

The comparison of clinical efficacy of antibiotic therapy in community pneumonia patients at the NTB Provincial Hospital showed that the combination of β-lactam and macrolide antibiotics was more effective than the use of single antibiotics [27]. The use of antibiotic drugs in pneumonia patients in hospitals emphasizes the importance of selecting the right therapy according to the patient's clinical condition to achieve optimal treatment outcomes [28].

(Ministry of Health of the Republic of Indonesia, 2017) the pneumonia management guidelines also recommend the use of combination antibiotics as one of the main approaches in the management of community pneumonia, especially in patients with a high risk of complications [29]. (Perhimpunan Dokter Paru Indonesia, 2022) also provides guidelines for the diagnosis and management of community pneumonia in Indonesia, which reinforces the use of combination antibiotics for patients with community pneumonia of moderate to severe severity [30].

The profile of antibiotic use in community pneumonia patients also supported the use of combination antibiotics, with a note that the profile of resistance to antibiotics must be considered [31]. Meanwhile, antibiotic treatment strategies for community-acquired pneumonia in adults suggested an evidence-based approach in the selection of optimal antibiotic therapy [32]. Another study conducted on the efficacy and safety of levofloxacin and ceftriaxone in the treatment of community-acquired pneumonia showed that both drugs were effective, but the combination with macrolides gave better results in some cases [33].

Guidelines published by the World Health Organization regarding the use of antibiotics in hospitals are also an important reference in determining the choice of antibiotic therapy for community pneumonia [34]. through its published guidelines, it provides more specific guidance on the use of combination antibiotics in adult patients with community pneumonia, which is the main reference in Indonesia.

A meta-analysis on the efficacy and safety of moxifloxacin and levofloxacin in the treatment of community pneumonia, which showed that both antibiotics have almost the same effectiveness, although combination with macrolides may provide additional benefits [35]. in their noninferiority trial, they compared β-lactam monotherapy with β-lactam-macrolide combination in the treatment of moderate severity community pneumonia, which showed that this combination was more effective in reducing the severity of disease in patients [36].

With the available evidence, it can be concluded that the use of a combination of β-lactam and macrolide antibiotics is an effective approach in the treatment of community pneumonia, especially in patients with moderate to severe severity. Further research and updates to clinical guidelines are needed to continue optimizing this

therapy, taking into account factors such as antibiotic resistance and the patient's clinical condition.

Additional side effects such as gastrointestinal disturbances, as well as the potential for increased antimicrobial resistance [13][21], further emphasize the need for a cautious approach. Therefore, a careful risk-benefit evaluation for each patient is required to ensure that the use of the β-lactam and macrolide combination is not only safe but also delivers optimal therapeutic outcomes. In compiling this review article, several limitations need to be noted. First, most of the articles and journals reviewed are from more than 10 years ago, which may affect the relevance and application of the results in the current medical practice, considering advances in the management of community-acquired pneumonia and shifts in antibiotic resistance patterns. Second, many of the articles and journals included in this review are not original research but are reviews or secondary analyses, which can limit the validity and strength of the evidence presented. These limitations should be considered when evaluating the findings and recommendations derived from this review article, as well as the importance of recent and original research to build a stronger evidence base.

Recent studies have consistently confirmed the effectiveness of β-lactam and macrolide combination therapy, especially in severe cases of community-acquired pneumonia (CAP). A meta-analysis involving 47 studies and 58,759 patients, found that this combination reduced 30-day mortality by 35% (OR 0.65; 95% CI 0.51–0.82) and improved clinical resolution by 23% (OR 1.23; 95% CI 1.00–1.52), particularly in infections caused by Streptococcus pneumoniae and Klebsiella pneumoniae [37]. The ACCESS randomized double-blind trial in Greece further supported these findings, showing higher early clinical response rates (68% vs 38% by day 4) and reduced inflammatory markers in patients receiving clarithromycin alongside β-lactam therapy [38]. Similarly, a prospective cohort study reported significantly lower 30-day mortality (16.7% vs 43.8%) in ICU patients treated with the combination, with an adjusted OR of 0.29 (95% CI 0.09–0.96) [39]. Moreover, a recent meta-analysis of six randomized controlled trials (RCTs) involving 2,661 patients found that while mortality differences were not significant, combination therapy yielded a higher treatment success rate than monotherapy (RR 1.17; 95% CI 1.04–1.32; p=0.009) [40].

Conclusion

The combination of β-lactam and macrolide antibiotics has been proven to be more effective than monotherapy or other combinations, particularly in severe community-acquired pneumonia (CAP). This combination reduces mortality, accelerates clinical recovery, and provides broad coverage against both typical and atypical pathogens, such as Mycoplasma pneumoniae and Chlamydophila pneumoniae. Macrolides also have immunomodulatory effects that help reduce systemic inflammation. Ceftriaxone or Ampicillin/Sulbactam are commonly used as β-lactams, combined with Azithromycin or Clarithromycin as macrolides, with the Ceftriaxone-Azithromycin combination being the most common due to its optimal pathogen coverage. The effectiveness of this combination also reduces 30-day readmission rates, improves patient quality of life, and aligns with the Indonesian Ministry of Health's recommendations as a primary treatment option for CAP.

Author's Contribution

Nurul Hikmah: responsible for the study design, literature review, and drafting of the manuscript. Mally Ghinan Sholih: interpretation of clinical outcomes.

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