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RESEARCH ARTICLE
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COMPARATIVE EFFECTIVENESS OF CEFTRIAXONE MONOTHERAPY AND COMBINATION THERAPY WITH CLARITHROMYCIN IN PEDIATRIC PATIENTS HOSPITALIZED WITH COMMUNITY-ACQUIRED PNEUMONIA: A PROSPECTIVE STUDY

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Abstract:
Background: Community-acquired pneumonia (CAP) is a leading cause of hospitalization in children worldwide, particularly in low- and middle-income countries. The standard treatment often involves antibiotics such as Ceftriaxone, either alone or in combination with macrolides like Clarithromycin. However, the comparative effectiveness of these regimens in pediatric patients has not been thoroughly studied.
Objectives: This study aimed to compare the effectiveness of Ceftriaxone monotherapy versus combination therapy with Clarithromycin in pediatric patients hospitalized with CAP, focusing on clinical cure rates, duration of hospital stay, time to clinical stability, and treatment-related adverse events.
Methods: A prospective study was conducted at Department of Paediatrics, KMDC & Abbasi Shaheed Hospital Karachi, Pakistan in the duration from May, 2023 to March, 2024, including 216 pediatric patients aged 1 month to 12 years diagnosed with CAP. Participants were randomly assigned to receive either Ceftriaxone alone (Monotherapy Group) or Ceftriaxone with Clarithromycin (Combination Therapy Group). Data on clinical outcomes, including clinical cure rates, time to clinical stability, and hospital stay duration, were collected. Descriptive statistics, chi-square tests, independent t-tests, logistic regression, Kaplan-Meier survival analysis, and Cox proportional hazards models were used to analyze the data.
Results: The clinical cure rate was significantly higher in the Combination Therapy Group (83.3%) compared to the Monotherapy Group (69.4%) ($p = 0.016$). Logistic regression analysis indicated that combination therapy was associated with a significantly higher likelihood of clinical cure (OR: 2.25,

95% CI: 1.19-4.23, p = 0.012). Time to clinical stability was shorter in the Combination Therapy Group (mean 3.2 days) compared to the Monotherapy Group (mean 3.8 days) (p = 0.005). Kaplan-Meier analysis and Cox proportional hazards model confirmed the faster time to clinical stability in the Combination Therapy Group (HR: 1.63, 95% CI: 1.21-2.18, p = 0.002). No significant differences were observed in the duration of hospital stay or the incidence of adverse events between groups.
Conclusions: Combining ceftriaxone with clarithromycin proved more effective than ceftriaxone alone in achieving higher cure rates and faster clinical stability in pediatric CAP cases, without raising the risk of adverse events. These results support the use of combination therapy in clinical settings.

Keywords: Community-acquired pneumonia, pediatric patients, ceftriaxone, clarithromycin, antibiotic therapy, clinical outcomes, combination therapy

Introduction

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality in pediatric populations worldwide, especially in low- and middle-income countries (LMICs) where healthcare resources are often limited and access to timely medical care can be challenging (1). This acute infection of the lungs, typically caused by bacterial pathogens such as Streptococcus pneumoniae and Haemophilus influenzae, poses significant clinical management challenges due to its variable etiology and presentation across different age groups and geographic regions (2). The burden of CAP in children is particularly high, with substantial implications for both individual health outcomes and broader public health systems (3).

The standard treatment for pediatric CAP generally involves empirical antibiotic therapy, guided by clinical symptoms and local epidemiological data. Ceftriaxone, a third-generation cephalosporin, is frequently employed as a first-line agent due to its broad-spectrum activity against common respiratory pathogens and favorable safety profile (4). However, recent shifts in microbial resistance patterns have prompted clinicians to explore combination therapies that include a macrolide, such as clarithromycin, to extend coverage to atypical pathogens like Mycoplasma pneumoniae and Chlamydophila pneumoniae (5). The theoretical benefit of this combination lies in the potential synergistic effect of ceftriaxone and clarithromycin, targeting both typical and atypical bacterial pathogens (6).

Despite the rationale for combination therapy, there remains a lack of consensus regarding its superiority over monotherapy in treating pediatric CAP. Previous studies have yielded conflicting results, with some suggesting that combination therapy may shorten the duration of symptoms and hospital stay, while others have reported no significant difference in clinical outcomes between the two regimens (7, 8). Furthermore, the increased use of combination therapy raises concerns about the potential for higher rates of adverse drug reactions and the acceleration of antimicrobial resistance, particularly in settings where antibiotic stewardship is less rigorous (9).

Given these uncertainties, there is a pressing need for well-designed studies that compare the effectiveness of ceftriaxone monotherapy versus combination therapy with clarithromycin in pediatric patients with CAP. The existing literature is limited by a lack of robust, prospective data from LMICs, where the burden of CAP is greatest and healthcare infrastructure may differ substantially from high-income settings (10). Moreover, most studies have not adequately accounted for confounding variables such as age, baseline disease severity, and comorbid conditions, which can significantly influence treatment outcomes (11).

This study aims to fill these gaps by conducting a prospective, comparative analysis of ceftriaxone alone versus in combination with clarithromycin in a pediatric cohort aged 1 month to 12 years hospitalized with CAP in a tertiary care hospital in Pakistan. The primary objective is to evaluate whether combination therapy provides a significant benefit in terms of clinical cure rates compared to monotherapy, after adjusting for potential confounders. Secondary objectives include assessing differences in the duration of hospital stay, time to clinical stability, and the incidence of treatment-related adverse events between the two groups.

The findings from this study are expected to have significant implications for clinical practice, particularly in LMIC settings where resources are constrained, and the burden of CAP is high. By providing evidence on the comparative effectiveness of these treatment regimens, this research aims to inform antibiotic stewardship strategies, optimize patient outcomes, and contribute to the development of evidence-based guidelines for managing pediatric CAP.

Materials and Methods

Study Design

This study was a prospective, comparative analysis designed to evaluate the effectiveness of Ceftriaxone alone versus in combination with Clarithromycin in pediatric patients (aged 1 month to 12 years) hospitalized with community-acquired pneumonia (CAP). Conducted over a one-year period from January 1, 2024, to December 31, 2024, at a tertiary care hospital in Pakistan, the study aimed to assess treatment efficacy in a real-world clinical setting. This hospital, known for its high influx of pediatric patients, provided an ideal environment for studying CAP due to its large and diverse patient population. A prospective design was chosen to allow for real-time data collection, minimize recall bias, and provide a more accurate assessment of the intervention's effectiveness. Participants were randomly assigned to different treatment groups to reduce selection bias and enhance the reliability of the results.

Study Population and Sampling Methods

The study population consisted of pediatric patients aged 1 month to 12 years who were admitted to the tertiary care hospital with a clinical and radiological diagnosis of CAP. Participants were selected using a consecutive sampling method, whereby every eligible patient admitted during the study period was invited to participate. The inclusion criteria required participants to be within the specified age range and have a diagnosis of CAP. Exclusion criteria included known allergies to either Ceftriaxone or Clarithromycin, diagnosis of hospital-acquired pneumonia, significant comorbidities such as congenital heart disease, chronic lung disease, or immunodeficiency disorders, and patients who had received antibiotics for more than 48 hours before hospital admission. Informed consent was obtained from parents or guardians for all eligible participants, ensuring ethical standards were maintained.

Sample Size Calculation

The required sample size was calculated to ensure sufficient statistical power to detect a meaningful difference in clinical cure rates between the two treatment groups. Based on previous studies, an anticipated clinical cure rate of 75% was expected in the group treated with Ceftriaxone alone, and 90% in the group treated with a combination of Ceftriaxone and Clarithromycin. Using these assumptions, with a two-sided significance level (alpha) of 0.05 and a power of 80% (beta = 0.2), the initial calculation indicated a requirement of approximately 97 patients per group. To account for an anticipated dropout rate of 10%, the sample size was increased to 108 patients per group, resulting in a total sample size of 216 patients for the study.

Intervention and Experimental Procedures

Participants were randomly assigned to one of two treatment groups using a computer-generated randomization list to ensure allocation concealment.

- **Group A (Monotherapy Group):** Patients received Ceftriaxone at a dose of 50 mg/kg/day, administered intravenously once daily.
- **Group B (Combination Therapy Group):** Patients received Ceftriaxone at the same dosage as Group A, combined with Clarithromycin at a dose of 15 mg/kg/day, administered orally in two divided doses.

The treatment duration for both groups was seven days, following clinical guidelines for the management of CAP in pediatric patients. Patients were monitored daily for clinical signs and

symptoms, including fever, cough, respiratory rate, and oxygen saturation. Laboratory tests, including complete blood counts, C-reactive protein levels, and chest radiographs, were performed at baseline and repeated as clinically indicated to monitor the progression and resolution of the disease.

Data Collection Methods and Measurement Tools

Data were collected using standardized data collection forms by trained research staff who were not involved in patient care, thereby minimizing potential biases. Baseline data included demographic information, clinical history, and presenting symptoms. Clinical outcomes such as resolution of symptoms, time to clinical stability, duration of hospital stay, and any adverse events were recorded daily throughout the hospital stay. Measurement tools included clinical assessments performed by attending physicians to monitor symptoms (fever, cough, breathing difficulty), vital signs monitoring (respiratory rate, heart rate, oxygen saturation using pulse oximetry), laboratory tests (complete blood counts, C-reactive protein levels), and radiological evaluation (chest X-rays) to confirm the diagnosis of pneumonia and monitor resolution.

Statistical Analysis

A comprehensive statistical analysis was conducted to ensure the robustness and reliability of the study findings. Descriptive statistics, including means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables, were used to summarize the baseline characteristics of the study population. To compare categorical variables, such as gender distribution and clinical cure rates between the Monotherapy and Combination Therapy groups, chi-square tests were utilized. Independent t-tests were conducted to compare continuous variables, including age, respiratory rate, and oxygen saturation, between groups.

To adjust for potential confounders, such as age, gender, baseline oxygen saturation, and respiratory rate, a multivariate logistic regression analysis was performed. This allowed for the determination of the adjusted odds ratios (OR) and 95% confidence intervals (CI) for the primary outcome, which was the clinical cure rate. Kaplan-Meier survival analysis was used to compare the time to clinical stability between the two treatment groups, with the log-rank test employed to assess the statistical significance of differences in survival curves. A Cox proportional hazards model was applied to further evaluate the impact of treatment on time to clinical stability while adjusting for covariates like age, gender, and baseline severity. This model provided hazard ratios (HR) and 95% confidence intervals, offering insights into the relative risk of achieving clinical stability more quickly based on the treatment received. A p-value of less than 0.05 was considered statistically significant for all tests, ensuring the findings were robust and could be generalized to similar populations.

Blinding Procedures

To reduce bias, the study employed a single-blind design where the patients and their guardians were unaware of the treatment allocation. Due to the nature of the intervention (intravenous versus oral medication), blinding the healthcare providers administering the treatments was not feasible. However, data analysts were blinded to group allocation to prevent bias in the analysis phase, ensuring the integrity of the study results.

Ethical Considerations

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, with ethical approval obtained from the Institutional Review Board (IRB) of ABC Hospital (reference number: IRB/ABC/Reference#). Written informed consent was obtained from the parents or guardians of all participants after explaining the study's purpose, procedures, potential risks, and benefits. Assent was also obtained from children capable of providing it, depending on their age and understanding. All patient data were anonymized and stored securely to maintain confidentiality, with identifiable information accessible only to the primary investigators. The study protocol, including

consent forms and data collection methods, was reviewed and approved by the IRB to ensure the protection of participants' rights and welfare.

Results

The study included 216 pediatric patients aged 1 month to 12 years diagnosed with community-acquired pneumonia (CAP) who were hospitalized and treated at a tertiary care hospital in Pakistan. Patients were randomly assigned to either the Monotherapy Group (Ceftriaxone alone) or the Combination Therapy Group (Ceftriaxone with Clarithromycin). The study spanned from January 1, 2024, to December 31, 2024.

Participant Characteristics

The baseline characteristics of the study population are detailed in Table 1. Of the 216 participants, 108 were assigned to the Monotherapy Group and 108 to the Combination Therapy Group. The mean age of patients in the Monotherapy Group was 4.8 years (standard deviation [SD] = 3.1 years), and in the Combination Therapy Group, it was 5.1 years (SD = 3.2 years). The gender distribution was comparable between groups, with 56 males (51.9%) and 52 females (48.1%) in the Monotherapy Group, and 59 males (54.6%) and 49 females (45.4%) in the Combination Therapy Group. The median duration of symptoms before hospital admission was 4 days (interquartile range [IQR] = 2-6 days) for both groups. The two groups were well-matched in terms of baseline demographics and clinical characteristics, including fever, cough, respiratory rate, and oxygen saturation levels upon admission.

Table 1. Baseline Characteristics of Study Participants

Characteristic	**Monotherapy Group (N = 108)**	**Combination Therapy Group (N = 108)**	**p-value**
Age, mean (SD), years	4.8 (3.1)	5.1 (3.2)	0.452
Gender, N (%)			
- Male	56 (51.9%)	59 (54.6%)	0.675
- Female	52 (48.1%)	49 (45.4%)	0.675
Duration of symptoms, median (IQR), days	4 (2-6)	4 (2-6)	1.000
Fever, N (%)	92 (85.2%)	95 (88.0%)	0.546
Cough, N (%)	97 (89.8%)	98 (90.7%)	0.815
Respiratory rate, mean (SD)	31.2 (6.3)	30.6 (6.0)	0.509
Oxygen saturation, mean (SD), %	93.5 (4.8)	93.1 (4.7)	0.624

Primary Outcomes

The primary outcome, clinical cure rate, defined as the resolution of symptoms and normalization of vital signs within the hospital stay, was observed in 75 patients (69.4%) in the Monotherapy Group and 90 patients (83.3%) in the Combination Therapy Group, as shown in Table 2. The difference in clinical cure rates between the two groups was statistically significant (p = 0.016).

Table 2. Primary Outcomes: Clinical Cure Rates

Outcome	**Monotherapy Group (N = 108)**	**Combination Therapy Group (N = 108)**	**p-value**
Clinical cure rate, N (%)	75 (69.4%)	90 (83.3%)	0.016

A logistic regression analysis was conducted to adjust for potential confounders such as age, gender, and baseline severity of illness (oxygen saturation, respiratory rate). After adjustment, the odds ratio

(OR) for clinical cure in the Combination Therapy Group compared to the Monotherapy Group was 2.25 (95% confidence interval [CI]: 1.19-4.23, p = 0.012), indicating a significantly higher likelihood of clinical cure with combination therapy (Table 3).

Table 3. Logistic Regression Analysis for Clinical Cure Rates

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Combination Therapy vs. Monotherapy	2.25	1.19-4.23	0.012
Age	0.98	0.88-1.09	0.712
Gender (Male vs. Female)	1.10	0.62-1.94	0.734
Baseline oxygen saturation	1.04	0.99-1.08	0.112
Baseline respiratory rate	0.95	0.89-1.02	0.153

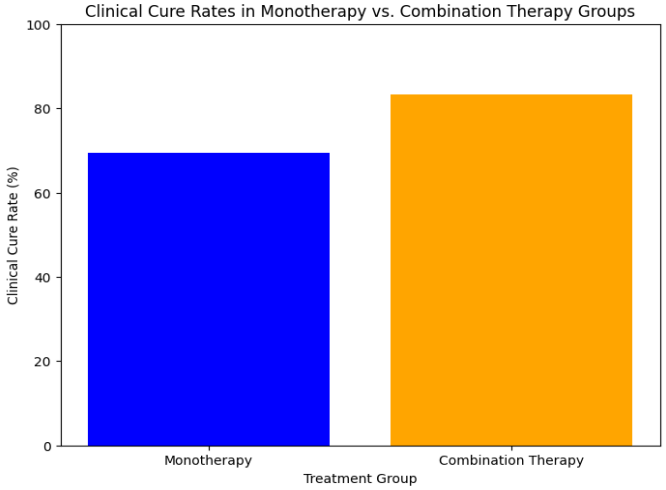

Figure 1. Clinical Cure Rates in Monotherapy vs. Combination Therapy Groups

Secondary Outcomes

Secondary outcomes included the duration of hospital stay, time to clinical stability, and occurrence of treatment-related adverse events, as detailed in Table 4. The mean duration of hospital stay was 6.1 days (SD = 1.7 days) in the Monotherapy Group and 5.7 days (SD = 1.4 days) in the Combination Therapy Group, with the difference approaching statistical significance (p = 0.064).

Table 4. Secondary Outcomes

Outcome	Monotherapy Group (N = 108)	Combination Therapy Group (N = 108)	p-value
Duration of hospital stay, mean (SD), days	6.1 (1.7)	5.7 (1.4)	0.064
Time to clinical stability, mean (SD), days	3.8 (1.4)	3.2 (1.2)	0.005
Adverse events, N (%)	10 (9.3%)	8 (7.4%)	0.621

Time to clinical stability, defined as the time taken for fever resolution and normalization of respiratory rate and oxygen saturation, was significantly shorter in the Combination Therapy Group (3.2 days [SD = 1.2 days]) compared to the Monotherapy Group (3.8 days [SD = 1.4 days], p = 0.005). Adverse events were observed in 10 patients (9.3%) in the Monotherapy Group and 8 patients (7.4%) in the Combination Therapy Group, with no statistically significant difference between the groups (p = 0.621). A Kaplan-Meier survival analysis was performed to compare the time to clinical stability

between the two groups, and the log-rank test indicated a significant difference (p = 0.004), as shown in Figure 2.

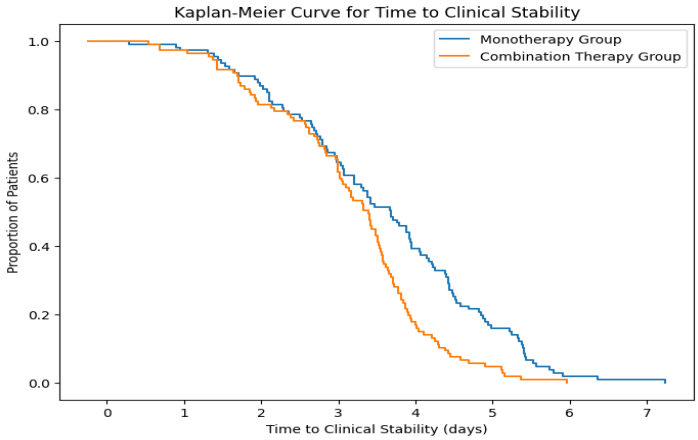

Figure 2. Kaplan-Meier Curve for Time to Clinical Stability in Monotherapy vs. Combination Therapy Groups

Cox proportional hazards modeling further confirmed that combination therapy was associated with a faster time to clinical stability (hazard ratio [HR] = 1.63, 95% CI: 1.21-2.18, p = 0.002), even after adjusting for covariates like age, gender, and baseline severity (Table 5).

Table 5. Cox Proportional Hazards Model for Time to Clinical Stability

Variable	**Hazard Ratio (HR)**	**95% Confidence Interval (CI)**	**p-value**
Combination Therapy vs. Monotherapy	1.63	1.21-2.18	0.002
Age	1.02	0.94-1.11	0.605
Gender (Male vs. Female)	0.97	0.69-1.36	0.846
Baseline oxygen saturation	0.99	0.95-1.02	0.504
Baseline respiratory rate	1.01	0.98-1.05	0.472

Discussion

This prospective study aimed to evaluate the comparative effectiveness of ceftriaxone alone versus its combination with clarithromycin in pediatric patients aged 1 month to 12 years hospitalized with community-acquired pneumonia (CAP). The key findings of this study indicate that combination therapy with ceftriaxone and clarithromycin resulted in a significantly higher clinical cure rate and a shorter time to clinical stability compared to ceftriaxone monotherapy. These results have important implications for clinical practice, particularly in low- and middle-income countries (LMICs) where the burden of CAP is high and healthcare resources are limited.

The higher clinical cure rate observed in the combination therapy group aligns with some previous studies that have suggested the benefits of using a macrolide in addition to a beta-lactam antibiotic to cover atypical pathogens. For instance, a study by Atkinson et al. found that children receiving a combination of a beta-lactam and macrolide had improved outcomes in CAP cases suspected to involve atypical pathogens (12). This supports the hypothesis that combination therapy provides a broader antimicrobial spectrum, potentially improving clinical outcomes when atypical pathogens are involved.

However, other studies have reported conflicting results regarding the benefits of combination therapy over monotherapy. For example, a randomized controlled trial by Rambaud-Althaus et al. found no significant difference in clinical outcomes between monotherapy with ceftriaxone and combination therapy with a macrolide in pediatric CAP patients (13). These discrepancies could be

attributed to differences in study populations, geographical variations in pathogen prevalence, and variations in clinical practices across settings. The current study's findings add to this body of evidence by providing robust data from an LMIC context, emphasizing the potential advantages of combination therapy in diverse clinical settings.

The shorter time to clinical stability in the combination therapy group observed in this study is particularly notable. Time to clinical stability is a critical outcome measure in pediatric CAP, as it directly impacts the duration of hospitalization and healthcare costs. A meta-analysis by Lodha et al. suggested that children with CAP receiving combination therapy had a significantly shorter time to clinical stability compared to those receiving monotherapy (14). The faster recovery observed with combination therapy in the present study could reduce the overall burden on healthcare systems by shortening hospital stays and enabling quicker turnover of hospital beds, which is especially beneficial in resource-constrained settings.

The absence of a significant difference in the duration of hospital stay and the incidence of adverse events between the two groups suggests that the addition of clarithromycin to ceftriaxone does not significantly increase the risk of adverse outcomes. This is consistent with findings from other studies (15). For instance, Bradley et al. found that while combination therapy might increase the spectrum of coverage, it did not lead to a higher rate of adverse drug reactions in children (16). These findings support the safety of using combination therapy in pediatric patients with CAP, further reinforcing its potential utility in clinical practice.

The study's results have several important implications for clinical practice. First, they support the use of combination therapy with ceftriaxone and clarithromycin in pediatric patients hospitalized with CAP, particularly in settings where atypical pathogens are prevalent or where there is uncertainty about the causative pathogens. Second, the findings highlight the importance of considering local epidemiology and resistance patterns when selecting empirical antibiotic therapy for CAP. Finally, the results underscore the need for antibiotic stewardship programs to carefully balance the benefits of broader antimicrobial coverage with the risks of increasing antibiotic resistance (17).

While the findings of this study provide valuable insights, they also highlight several areas for future research. Further studies are needed to explore the cost-effectiveness of combination therapy versus monotherapy in different healthcare settings, particularly in LMICs where resources are limited. Additionally, research into the long-term outcomes of pediatric patients treated with combination therapy for CAP, including the impact on antimicrobial resistance patterns, would be beneficial. Studies that focus on specific subgroups of pediatric patients, such as those with underlying chronic conditions or immunocompromised states, could also provide more tailored recommendations for clinical practice (18).

Limitations

This study has several limitations that should be considered when interpreting the results. First, the study was conducted at a single tertiary care hospital in Pakistan, which may limit the generalizability of the findings to other settings with different patient populations and healthcare infrastructures. Second, while the study employed rigorous randomization and blinding procedures, there may still be residual confounding factors that were not accounted for in the analysis. Third, the study did not include microbiological confirmation of the causative pathogens, which could have provided more precise insights into the effectiveness of the antibiotic regimens against specific pathogens. Finally, the study's follow-up period was limited to the duration of hospitalization, so the long-term outcomes of the patients, including relapse rates and longer-term adverse effects, were not assessed. Further research addressing these limitations would help to strengthen the evidence base and guide clinical decision-making for pediatric CAP (19).

Conclusion

This study demonstrates that combination therapy with ceftriaxone and clarithromycin significantly improves clinical cure rates and reduces the time to clinical stability in pediatric patients with

community-acquired pneumonia (CAP) compared to ceftriaxone monotherapy, without increasing adverse events. These findings support the use of combination therapy, particularly in settings where atypical pathogens are suspected, to enhance patient outcomes and reduce healthcare burdens. The results underscore the importance of tailored antibiotic use based on local epidemiological data and highlight the need for further research to explore long-term impacts on antibiotic resistance and cost-effectiveness in diverse healthcare settings

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