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ARCHIVES OF Pulmonology and Respiratory Care OPEN ACCESS JOURNAL

ISSN: 2581-3684 DOI: https://dx.doi.org/10.17352/aprc

Research Article

Analysis of the Efficacy of Erythromycin Cyclic 11,12-Carbonate Combined with Azithromycin in the Treatment of Severe Mycoplasma Pneumoniae Pneumonia in Children and its Effect on Cytokines

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Received: 21 August, 2024
Accepted: 26 August, 2024
Published: 27 August, 2024

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Keywords: Severe mycoplasma pneumoniae pneumonia; Children; Erythromycin cyclic 11,12-carbonate; Azithromycin

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Abstract

Introduction: Mycoplasma Pneumoniae Pneumonia (MPP) is an inflammation of the lungs caused by Mycoplasma pneumoniae infection. Macrolide antibiotics are the therapeutic agents of choice for MPP. This study aimed to explore the efficacy of erythromycin cyclic 11,12-carbonate combined with azithromycin in treating children with severe Mycoplasma pneumoniae pneumonia (SMPP).

Methods: 84 children with SMPP treated at Hubei Maternal and Child Health Hospital between February 2021 and December 2021 were randomly divided into two groups. The control group was treated with intravenous azithromycin and then changed to oral azithromycin. The experimental group was treated with intravenous azithromycin and then switched to oral erythromycin cyclic 11,12-carbonate. The clinical efficacy, symptom improvement, inflammatory levels, and cytokine levels before and after treatment were compared, and the occurrence of adverse reactions was recorded.

Results: The overall effective rate of treatment in the experimental group was significantly higher than that in the control group ($P<0.05$). The time to the disappearance of clinical symptoms and length of hospitalization of the experimental group was significantly shorter than that of the control group ($P<0.05$). After treatment, inflammatory levels and cytokine levels of the experimental group were significantly lower than those of the control group ($P<0.05$). There was no difference in the incidence of adverse reactions between the two groups ($P>0.05$).

Conclusion: Erythromycin cyclic 11,12-carbonate combined with azithromycin in the treatment of children with SMPP had significant efficacy, superior to azithromycin monotherapy, which could effectively improve immune function and clinical symptoms.

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Abbreviations

MPP: Mycoplasma Pneumoniae Pneumonia; MP: Mycoplasma Pneumoniae; RMPP: Refractory Mycoplasma Pneumoniae Pneumonia; SMPP: Severe Mycoplasma Pneumoniae Pneumonia; LDH: Lactate Dehydrogenase; CRP: C-reactive Protein; ESR: Erythrocyte Sedimentation Rate; HGF: Hepatocyte Growth Factor; TNF-α: Tumor Necrosis Factor-α; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-10: Interleukin-10; MRMP: Macrolide-Resistant Mycoplasma Pneumonia

Introduction

Mycoplasma Pneumoniae Pneumonia (MPP), an inflammatory disease of the lungs, arises from infection by Mycoplasma Pneumoniae (MP). Epidemiological data indicated that MPP comprised over one-third of non-bacterial pneumonia cases [1] and accounted for 32.4%-39.5% of pediatric hospitalizations due to community-acquired pneumonia in China [2,3]. Notably, 7%-36% of children infected with MP experienced extrapulmonary complications [4], affecting virtually all extrapulmonary systems. MPP exhibits a diverse spectrum of clinical presentations and may progress to Refractory Mycoplasma Pneumoniae Pneumonia (RMPP) or Severe Mycoplasma Pneumoniae Pneumonia (SMPP), with disease severity correlating positively with elevated cytokine levels [5].

Currently, pharmacological intervention, particularly with macrolide antibiotics, is the primary therapeutic approach for MPP. Given the absence of a standardized treatment protocol for SMPP in pediatric patients, this study aimed to investigate the effectiveness of applying erythromycin cyclic 11,12-carbonate combined with azithromycin in the treatment of children with SMPP as well as the effects on the regulation of inflammatory factors and cytokines.

Materials and methods

Study patients

This study enrolled 84 pediatric patients diagnosed with SMPP admitted to Hubei Maternal and Child Health Hospital between February 2021 and December 2021. Inclusion criteria were based on the confirmation of MPP and fulfillment of at least two of the first three or any one of the last two of the following criteria for SMPP [6]: (1) evident dyspnea or tachycardia (age-specific thresholds applied) with or without hypotension, triple concave sign, and cyanosis; (2) inefficacy of standard macrolide antibiotic therapy for over a week, as indicated by persistent fever (≥38.5°C) or unimproved/worsened lung imaging, or fever lasting ≥10 days; (3) chest imaging revealing large patchy shadows involving ≥1 segment or lobe; (4) presence of pleural effusion, atelectasis, necrotizing pneumonia/pulmonary abscess, or other intrapulmonary complications; (5) severe hypoxemia (PaO_2<60 mmHg) or concomitant severe dysfunction of other systems (e.g., central nervous system infection, heart failure, myocarditis, gastrointestinal hemorrhage). Exclusion criteria encompassed: (1) co-infections with primarily other systemic infectious diseases; (2) allergy to study medications; (3) congenital immunodeficiency; (4) recent exposure to other drug therapies.

The study was reviewed and approved by the Ethics Committee of Hubei Maternal and Child Health Hospital, with the ethical approval number 2020-IEC-XM048. Written informed consent was obtained from the parents/guardians of all participating children.

Study drugs

Patients were randomized into a control group (n=40) and an experimental group (n=44). Randomization was achieved using the Random Number Table Method. Patients were allocated unique identifiers, followed by the random selection of a commencement point and reading orientation within a computer-generated random number sequence. The sequence was then read in an established order, correlating the generated numbers with patient identifiers to execute the randomization process effectively.

All patients were admitted to the hospital for bed rest and received symptomatic therapy, including antipyretics, anti-inflammatory drugs, and expectorants. Nebulized inhalation and fluid replenishment were provided as part of the treatment, with oxygen therapy administered when necessary. Nursing care was intensified to ensure patient well-being. Patients were strictly prohibited from using antibiotics other than those prescribed in their treatment regimen.

The control group received azithromycin monotherapy. Initially, azithromycin (Pfizer Pharmaceuticals Ltd., 0.1 g) diluted with 0.9% sodium chloride solution was administered intravenously at a dose of 10 mg/kg per day for 3 consecutive days. When the clinical signs of infection improved and the condition was essentially stable, the same dose (10 mg/kg per day) of azithromycin was switched to oral administration for another 7 consecutive days.

The experimental group received a combination of erythromycin cyclic 11,12-carbonate and azithromycin. First, the intravenous drip regimen of azithromycin, including the dosage and administration method, was the same as that of the control group. When the clinical signs of infection improved and the condition was essentially stable, erythromycin cyclic 11,12-carbonate (Bright Future Pharmaceutical Lab. Ltd.) was administered orally at a dose of 15 mg/kg twice daily for seven consecutive days.

Clinical evaluation

(1) **Clinical response:** The efficacy was evaluated based on the following criteria [7]. Cure: Laboratory examination shows normalization of white blood cell count, with near-complete resolution of symptoms. Marked Improvement: Laboratory examination reveals normalization of white blood cell count, accompanied by significant improvement in symptoms. Improvement: A notable decrease in white blood cell count, though still above normal range, with some alleviation of

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symptoms. Failure: No change in white blood cell count or symptoms.

The overall effective rate was calculated as the sum of the cure, marked improvement, and improvement rates.

(2) Recovery: The time to disappearance of clinical symptoms (antipyretic time, cough disappearance time, rales disappearance time, lung shadow disappearance time) and length of hospitalization were compared between the two groups.

(3) Inflammatory levels: Levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured to evaluate the inflammatory status.

(4) Cytokine levels: Hepatocyte growth factor (HGF), tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), interleukin-6 (IL-6), and interleukin-10 (IL-10) were assessed to investigate the immune response.

(5) Adverse reactions: Gastrointestinal disturbances and skin rashes were recorded.

Before treatment and on the 7th day of treatment, 4 ml of elbow venous blood was collected in the early morning on an empty stomach from the two groups of children. The samples were packed in dry test tubes and centrifuged at 3000 rpm for 5 minutes after 1-hour incubation at room temperature. Supernatants were stored in sterile microcentrifuge tubes at -80°C until analysis within 48 hours, using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Ruifan Biotechnology Co.). ELISA was used to detect HGF, TNF-α, IL-4, IL-6, and IL-10 in the two groups.

Statistical analysis

Statistical analyses were conducted using SAS Enterprise 7.15. For categorical variables, count data were presented in the format of [number of patients (%)], and intergroup comparisons were assessed using the chi-square (χ^2) test. For continuous variables that adhered to a normal distribution, they were reported as the mean±standard deviation (Mean±SD), and comparisons between groups were performed with the Student's t-test. Statistical significance was defined as a p-value less than 0.05.

Result

A total of 84 patients were randomized to the two treatment groups: 44 in the experimental group received azithromycin combined with erythromycin cyclic 11,12-carbonate sequential therapy and 40 in the control group received azithromycin monotherapy. The baseline characteristics of the patients are summarized in Table 1. No statistically significant differences were observed between the two groups regarding sex, age, days of illness at presentation, inflammation levels, and cytokine levels (all P>0.05, Table 1). All patients were tested for COVID-19 and shown to be uninfected.

Table 2 shows the clinical responses of the two groups after treatment. The percentage of patients cured or improved after treatment was 92.68% in the experimental group and 70.00% in the control group (Table 2). The overall effective rate of treatment in the experimental group was significantly higher than that in the control group (**χ^2=5.866, P=0.027, Table 2).**

In terms of the relief of clinical symptoms of the patients after treatment, the experimental group had a faster recovery, which was manifested by a significantly shorter time for fever reduction, disappearance of cough, disappearance of rales, and disappearance of lung shadows (all P<0.05, Table 3). In addition, the hospitalization time of the experimental group was significantly shorter than that of the control group (10.17±1.52 vs 12.46±1.96, t=6.653, P=0.016, Table 3).

Table 1: Baseline characteristics of patients.

Characteristics	Experimental group, n=44	Control group, n=40
Sex (n (%))		
Male	23 (52.27)	21 (52.50)
Female	21 (47.73)	19 (47.50)
Age (years)		
Mean ± SD	7.06 ± 2.32	6.89 ± 2.54
Range	3.00 - 12.00	3.00 - 11.00
Days of illness at presentation (days)		
Mean ± SD	14.17 ± 1.62	14.57 ± 1.68
Range	7.00 - 23.00	6.00 - 23.00
Inflammation parameters (Mean ± SD)		
hs-CRP (mg/L)	27.84 ± 1.21	26.85 ± 1.18
LDH (U/L)	342.83 ± 89.85	358.37 ± 87.66
ESR (mm/h)	50.45±1.76	52.06±1.58
Cytokine parameters (Mean ± SD)		
HGF (pg/ml)	1238.65 ± 153.23	1307.28 ± 160.46
TNF-α (pg/ml)	1.12 ± 0.56	1.19 ± 0.48
IL-4 (pg/ml)	31.82 ± 4.93	32.07 ± 4.32
IL-6 (pg/ml)	14.37 ± 1.63	15.05 ± 1.22
IL-10 (pg/ml)	75.54 ± 17.98	73.55 ± 16.79

Data were shown as several patients (%) or Mean ± SD. The chi-square (χ^2) test and the student's t-test were applied. All P>0.05.
CRP: C-reactive Protein; LDH: Lactate Dehydrogenase; ESR: Erythrocyte Sedimentation Rate; HGF: Hepatocyte Growth Factor; TNF-α: Tumor Necrosis Factor-α; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-10: Interleukin-10.

Table 2: Clinical response after treatment.

Clinical response	Experimental group, n=44	Control group, n=40
Cure	23 (52.27)	11 (27.50)
Marked improvement	9 (20.45)	6 (15.00)
Improvement	9 (20.45)	11 (27.50)
Failure	3 (6.80)	12 (30.00)
Overall effective rate*	92.68%	70.00%

Data were shown as number of patients (%).
* The overall effective rate was calculated as the sum of the cure, marked improvement, and improvement rates. The chi-square (χ^2) test was applied.
χ^2=5.866, P=0.027.

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Before treatment, there was no statistically significant difference in the levels of hs-CRP, LDH, and ESR between the two groups (all $P>0.05$, Table 1). However, after treatment, statistically significant decreases in the levels of these inflammatory markers were observed in each group compared to baseline levels (all $P<0.05$). Notably, post-treatment levels of hs-CRP, LDH, and ESR were significantly lower in the experimental group compared to the control group (all $P<0.05$, Figure 1).

Similar findings were observed for cytokine levels. Pre-treatment analysis revealed no statistically significant differences in the levels of cytokines (HGF, TNF-α, IL-4, IL-6, IL-10) between the two groups (all $P>0.05$, Table 1). However, there was a significant decrease in the levels of each cytokine in each group after treatment compared to before treatment (all $P<0.05$). Importantly, cytokine levels in the experimental group were significantly lower than those in the control group after treatment (all $P<0.05$, Figure 2).

Adverse reactions, including gastrointestinal and skin symptoms, that occurred during treatment were recorded. The total incidence of adverse reactions was 13.64% in the experimental group and 17.50% in the control group, and the difference between the two groups was not statistically significant ($\chi^2=0.483$, $P=0.572$, Table 4).

Table 3: Time to disappearance of clinical symptoms and length of hospitalization.

Time (days)	Experimental group, n=44	Control group, n=40	*t*	*P*
Antipyretic time	3.06 ± 0.56	3.64 ± 0.83	2.886	0.032
Cough disappearance time	13.12 ± 1.88	15.84 ± 2.01	7.539	0.015
Rales disappearance time	6.38 ± 1.42	7.27 ± 1.57	7.163	0.021
Lung shadow disappearance time	9.32 ± 1.76	10.68 ± 2.05	7.316	0.028
Hospitalization time	10.17 ± 1.52	12.46 ± 1.96	6.653	0.016

Data were shown as Mean ± SD. Student's t-test was applied.

Discussion

The pathogenesis of SMPP is complex, including mixed infections and direct microbial invasion. MP, devoid of a cell wall, exhibits unique susceptibility to antibiotics that disrupt microbial protein synthesis, particularly macrolides, tetracyclines, and quinolones. However, given the constrained utilization of tetracyclines and quinolones in pediatric care due to safety concerns, macrolides have emerged as the primary therapeutic option for MPP in children.

Widespread use of azithromycin, a macrolide antibiotic, has gradually led to a surge in MP resistance, posing challenges

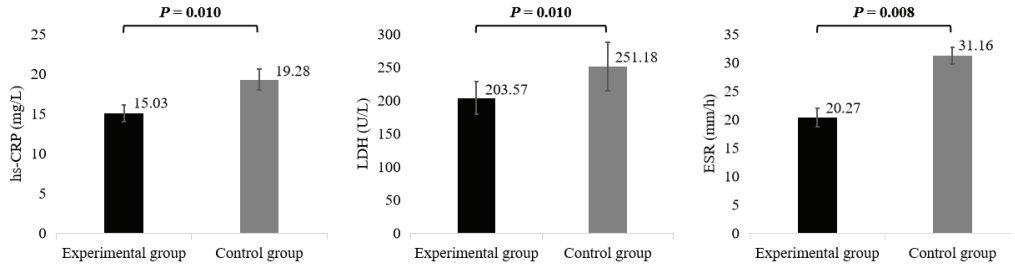

Figure 1: Comparison of mean inflammation levels between the two groups after treatment.
Student's t-test was applied. CRP: C-reactive Protein; LDH: Lactate Dehydrogenase; ESR: Erythrocyte Sedimentation Rate.

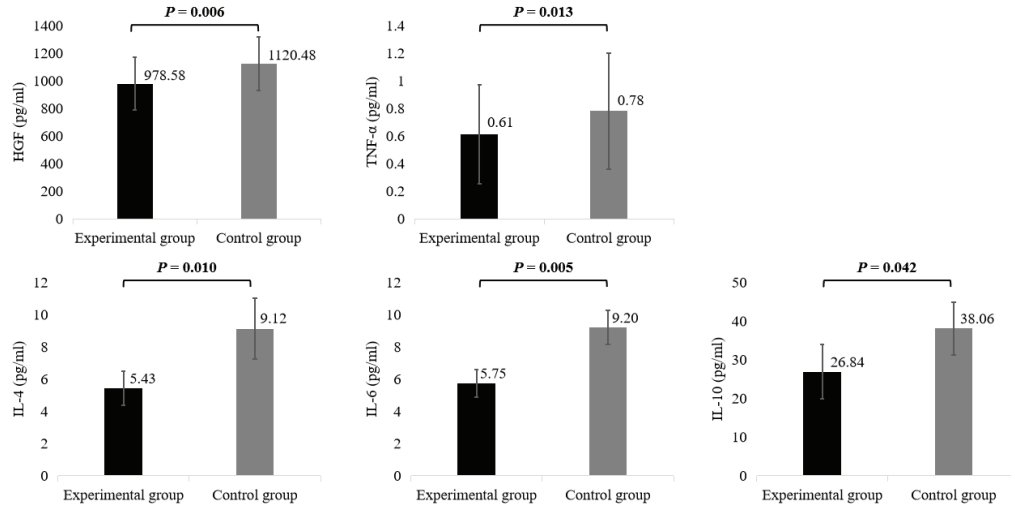

Figure 2: Comparison of mean cytokine levels between the two groups after treatment.
Student's t-test was applied. HGF: Hepatocyte Growth Factor; TNF-α: Tumor Necrosis Factor-α; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-10: Interleukin-10.

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Table 4: Adverse reactions in the two groups.

Adverse reactions	Experimental group, n=44	Control group, n=40
Emesis	0 (0.00)	1 (2.50)
Nausea	2 (4.55)	3 (7.50)
Diarrhea	3 (6.82)	3 (7.50)
Rash	1 (2.27)	0 (0.00)
Total incidence rate*	13.64%	17.50%

Data were shown as number of patients (%). *Chi-square (χ^2) test was applied. χ^2=0.483, P=0.572.

in selecting effective treatments for infected children. Azithromycin resistance in MP stands as a pivotal contributor to the occurrence of SMPP. Globally, the incidence of macrolide-resistant Mycoplasma pneumonia (MRMP) has soared, with particularly alarming rates observed in Asia, including 90%-100% in China, 87% in Japan, and 84.6% in South Korea [8]. Conversely, prevalence rates remained relatively lower in Europe and the United States, with 13% in the US, 26% in Italy, and 19% in Scotland [8].

Current research posited that the most significant mechanism of azithromycin resistance arose from the primary binding of macrolide antibiotics to the V region of the 23S rRNA structural domain within the 50S subunit of the MP ribosome. This binding inhibited the synthesis of MP proteins. Mutations occurring in this crucial V region led to a diminished affinity of azithromycin for the ribosome, ultimately resulting in resistance in MP. The clinical significance of SMPP has not yet been clarified, and clinically, it might be associated with drug-resistant bacterial infections [9,10]. Several studies demonstrated that SMPP was associated with prolonged fever, prolonged hospitalization, and prolonged antibiotic use and that patients had a higher frequency of pneumonia exacerbations and a greater likelihood of extrapulmonary complications [9]. These findings underscored the need for further investigation into the pathogenesis and optimal management strategies for SMPP.

The efficacy of combined low-dose glucocorticoids in treating SMPP was widely acknowledged [10-12]. The use of antimicrobial drugs is still being explored, and studies have been conducted on azithromycin in combination with tetracyclines or quinolones for the treatment of SMPP. Fangfang Dai et al. reported resistance in all six SMPP cases studied, noting that five patients achieved normal body temperature within 1-2 days post-combined azithromycin and levofloxacin treatment, accompanied by imaging improvement in four cases [13]. Ti-An Tsai emphasized the need for graded treatment strategies in pediatric MPP, advocating for tetracycline or quinolone combinations in SMPP management [10]. However, the use of these drugs in children is constrained by toxicity concerns. Tetracyclines are limited to children aged ≥8 years due to risks of tooth discoloration and enamel hypoplasia, with reported incidence ranging from 23% to 92%, dependent on dose and duration [14-19]. The use of quinolones in children is usually for specific indications because of their potential musculoskeletal toxicity. They were only approved by the FDA for the treatment and prophylaxis of complicated urinary tract infections, pyelonephritis, and inhalational anthrax in children under 18 years [20]. A study in juvenile animals showed erosive arthropathy in weight-bearing joints with the use of quinolones [21].

Considering the growth and development of children with MPP, the clinical treatment of SMPP may involve macrolide antibiotics, alone or in combination. There may be a synergistic effect when antibiotics are used in combination, with the combined effect of the two drugs being greater than the sum of the effects of each used alone. In addition, antibiotic combinations may slow the development of resistance. Some studies have shown that the development of resistance may be reduced when antibiotics are used in combination compared to single antibiotics [22,23]. Jiandi Li et al. demonstrated that the combination of erythromycin and azithromycin significantly enhanced therapeutic outcomes in pediatric MP infections [24]. However, erythromycin's instability in acidic environments predisposed it to decomposition, often eliciting gastrointestinal adverse effects. Furthermore, erythromycin typically necessitated high doses, slow infusions, and prolonged treatment courses, which led to injection site pain, phlebitis, and poor patient compliance due to difficulties in adhering to the regimen [25]. In contrast, erythromycin cyclic 11,12-carbonate, by incorporating a cyclic carbonate group into the erythromycin ring, exhibited greater stability in acidic environments, improved lipophilicity, and enhanced bioavailability, with antimicrobial activity 2-4 times that of erythromycin. Consequently, it might be a viable alternative to erythromycin in combined SMPP treatments.

Our study showed that while receiving similar symptomatic treatments, azithromycin combined with erythromycin cyclic 11,12-carbonate (experimental group) exhibited superior efficacy in the treatment of SMPP compared with azithromycin monotherapy (control group). Specifically, the experimental group showed significantly shorter antipyretic time, cough disappearance time, rales disappearance time, lung shadow disappearance time, and length of hospitalization, with all differences attaining statistical significance. Before treatment, no statistically significant difference was observed in CRP, ESR, and LDH levels between the two groups. However, post-treatment, the experimental group showed more pronounced reductions in CRP, ESR, and LDH, with these differences also reaching statistical significance. These findings suggested that erythromycin cyclic 11,12-carbonate, a 14-membered macrolide antibiotic, possessed anti-inflammatory properties [26].

Previous studies documented that MP triggered neutrophil activation and elicited both cellular and humoral immune responses in the host [27]. Elevated levels of cytokines, including HGF, IL-4, IL-6, IL-10, and TNF-α, have been detected in patients with SMPP [28-30], and these immunological abnormalities might contribute to the escalation of inflammation [31]. Notably, our study found no statistically significant difference in the baseline levels of these cytokines between the two groups before treatment. However, post-treatment, the experimental group, which received azithromycin combined with erythromycin cyclic

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11,12-carbonate, exhibited significantly greater reductions in cytokine levels compared to the control group treated with azithromycin monotherapy. The findings underscored the potential superiority of erythromycin cyclic 11,12-carbonate in mitigating inflammatory responses, possibly attributed to its higher concentration in lung and bronchial secretions, a 1.37-fold higher bioavailability than azithromycin, and enhanced penetration into phagocytic cells, thereby fostering a more potent immune synergy [32].

In analyzing adverse reactions, no statistically significant disparity was observed in their incidence rates between the experimental and control groups. Adverse reactions were focused on the digestive system, with symptoms including nausea, vomiting, and diarrhea, manifesting as thin and pasty stools without mucus or blood, or non-projectile vomiting of gastric contents without bile. Symptoms were mild and did not last long, typically resolving after discontinuation of the medication. Macrolides as motilin receptor agonists can cause gastrointestinal smooth muscle contractions and spasms. They may also induce intestinal wall alterations and mucosal inflammatory changes through neural reactions in the intestinal wall, thereby increasing gland secretion and the release of mediators such as histamine, serotonin, cholinergic agonists, and substance P, leading to gastrointestinal reactions like abdominal pain, diarrhea, nausea, and vomiting [33]. Furthermore, all patients underwent a 6-month outpatient follow-up. Review of chest imaging and pulmonary function (at 1 month, 3 months, and 6 months) were unremarkable. Some patients who had obstructive ventilation dysfunction on review returned to normal after nebulization therapy.

There were some limitations in our study. First, it was a single-center study with a relatively small sample size, which might affect the generalizability of the findings. Then, the study only included some of the inflammatory markers and cytokines, which may not provide a broader understanding of the inflammatory features of the disease. Finally, the follow-up period was only six months, which limited our observations to short-term outcomes and did not provide insight into long-term clinical prognosis. Future research with larger cohorts, more biomarker assessments, and longer follow-up periods was needed.

However, our study provided valuable insights into future directions for treatment. In particular, the combination of erythromycin cyclic 11,12-carbonate and azithromycin might offer a new strategy for the treatment of SMPP. This potential therapeutic approach could take advantage of the different pharmacologic profiles of both drugs to target resistant strains and modulate immune responses, thereby improving patient outcomes. Future studies should focus on refining this combination therapy and evaluating its safety, efficacy, and long-term impact in a broader clinical context.

Conclusion

In conclusion, the efficacy of erythromycin cyclic 11,12-carbonate combined with azithromycin in the treatment of SMPP was remarkable, which could effectively improve the immune function, reduce the level of inflammatory factors, and shorten the disappearance time of clinical symptoms to promote the early recovery of the patients.

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Citation: Dong R, Li J, Wu J, Hu W, Yan L, Le J. Analysis of the Efficacy of Erythromycin Cyclic 11,12-Carbonate Combined with Azithromycin in the Treatment of Severe Mycoplasma Pneumoniae Pneumonia in Children and its Effect on Cytokines. Arch Pulmonol Respir Care. 2024;10(1):016-022. Available from: https://dx.doi.org/10.17352/aprc.000087