

# Retrospective Analysis of Three Different Methods for the Treatment of Macrolide-Unresponsive Mycoplasma Pneumoniae Pneumonia in Children

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**Abstract:** Mycoplasma pneumoniae (MP) is an important cause of community-acquired pneumonia in children and adolescents. We screened 52 children with macrolide-unresponsive Mycoplasma pneumoniae pneumonia hospitalized at our institution from April 2023 to August 2023, and counted and evaluated their treatment modalities and efficacy. Based on the three different drug treatments, we divided all the children into four groups: Group A was the azithromycin oral sequential + glucocorticoid treatment effective group; Group B was the doxycycline oral treatment effective group; Group C was the doxycycline oral + glucocorticoid effective group. By  $\chi^2$  test, Kruskal-Wallis test, and ann-WhitneyU rank-sum test, we compared the effective cure rate, adjusted hospitalization days, effective fever recovery time, and pulmonary imaging regression under different treatment modalities. We chose three groups of treatment effective cases, A, B and C to analyze. There was no statistically significant difference in the effective cure rate among the three effective groups,  $P > 0.05$ ; There was a statistically significant difference in the number of adjusted hospitalization days,  $p < 0.05$ ; There was a statistical difference in the number of adjusted hospitalization days between groups A and B,  $P < 0.05$ ; There was a statistical difference in the number of adjusted hospitalization days between groups A and C,  $P < 0.05$ ; There was no statistically significant difference in the number of adjusted hospitalization days between groups B and C,  $P > 0.05$ ; There was no statistical difference in effective temperature recovery time or lung imaging outcomes among the three groups. From the study, we conclude that the choice of doxycycline or doxycycline and hormone therapy can shorten the number of days of hospitalization and achieve clinical cure more quickly.

**Keywords:** Macrolide-Unresponsive Mycoplasma Pneumoniae Pneumonia, Doxycycline, Azithromycin, Glucocorticoid

## 1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a common respiratory infection in pediatrics, accounting for about 10% to 40% of hospitalized children with community-acquired pneumonia [1, 2]. In 2023, the Chinese Center for Disease Control and Prevention released the monitoring data of respiratory tract infection in China for 11 years, among which children ranked first with a positive rate of 30.2%, and respiratory tract infection of preschool children caused by mycoplasma pneumoniae (MP) was as high as 56.7% [3]. In recent years, with the increase of MP infection rate, the incidence of severe mycoplasma pneumoniae (SMPP) in

children also shows an increasing trend year by year. According to the clinical symptoms and treatment response of Mycoplasma pneumoniae in children, the National Health Commission proposed the concept of macrolide-unresponsive mycoplasma pneumonia (MUMPP) in the Guidelines for Diagnosis and Treatment of Mycoplasma pneumoniae pneumonia in Children (2023 edition) [4]. Early identification of high-risk children with MPP, reasonably avoid the disease to refractory mycoplasma pneumoniae pneumonia (RMPP), severe mycoplasma pneumoniae pneumonia (SMPP) development. This study analyzed MUMPP inpatient cases to understand and evaluate the difference in therapeutic effect under different treatment modalities.

## 2. Methods

Fifty-two children with MUMPP admitted to the pediatric inpatient ward of the First Affiliated Hospital of Yangtze University from April 2023 to August 2023 were selected as the study objects. Diagnostic criteria refer to the Guidelines for Diagnosis and Treatment of Mycoplasma pneumoniae pneumonia in Children (2023 edition) and diagnostic criteria for MUMPP [4]: After 72 hours of orthodox treatment with macrolide antibiotics, the child with mycoplasma pneumoniae pneumonia continued to have fever, and the clinical signs and lung imaging showed no improvement or further aggravation of MPP. The clinical manifestations were fever and cough, pulmonary imaging supported pneumonia, and etiological or serological examination supported MP infection. Inclusion criteria: Meeting the diagnostic criteria, the patient's family members gave informed consent and signed the informed consent for glucocorticoid use, and the family members of patients younger than 8 years old gave informed consent and signed the informed consent for special treatment of doxycycline. Exclusion criteria: other bacterial and viral pneumonia were excluded; Except acute attacks of bronchial asthma in children; Except for the recurrence of disease caused by other factors in the treatment.

Information such as gender, age, duration of fever before admission, medication and other treatments, temperature recovery time after admission, lung imaging data and hospitalization duration were collected from the hospital case system. All 52 children were treated with oxygen inhalation, atomization, phlegm reduction and fever reduction if necessary. Differential treatment: Treatment was divided into three different modalities: (A) sequential oral azithromycin + glucocorticoid drops (B) oral doxycycline (C) oral doxycycline + glucocorticoid drops. Azithromycin tablets or azithromycin dry suspension (10mg/kg/ time, 1 time/day for children weighing less than 25kg, 0.25g/ time, 1 time/day for children weighing more than 25kg) sequential oral administration (5-7 days for the first course of oral administration, 3 days for the second course of oral administration, 3 days for the third); Methylprednisolone sodium succinate 1mg/kg/ time, 2 times/day; Or dexamethasone 0.3mg/kg/ time, 1 time/day; Glucocorticoid use time 3-7 days. Doxycycline tablet dosage: 2mg/kg/ time, Q12h, 10 days as the treatment course.

SPSS 27.0 was used for data processing. For measurement data, the Mean $\pm$ SD (Mean $\pm$ SD) was used to represent the normal distribution, while the median (interquartile distance) [M (P25, P75)] was used to represent the non-normal distribution, and the count data was used to represent the rate or component ratio (%). Treatment response rate, age, gender, lung imaging type, and lung imaging outcomes were compared between groups using  $\chi^2$  test; effective hospitalization days, effective thermal regression time, and total thermal duration were compared by Kruskal-Wallis test; and comparison between groups was performed by Mann-WhitneyU rank sum test. Bilateral  $P < 0.05$  was considered statistically significant.

## 3. Results

A total of 52 MUMPP children were included, including 32 males (61.5%) and 20 females (38.5%). The age of onset was  $7.3 \pm 2.9$  years. All patients received orthodox azithromycin oral therapy before and after hospitalization and still had persistent fever and cough without relief for 3 days or more. 22 cases were treated with oral azithromycin sequential + glucocorticoid therapy, 18 cases were effective and successfully cured, 4 cases were ineffective and changed to oral doxycycline + glucocorticoid therapy. Doxycycline oral therapy was used in 23 cases, 19 cases were effective and successfully cured, and 4 cases were ineffective and changed to doxycycline oral + glucocorticoid therapy. 7 cases were treated with doxycycline orally plus glucocorticoid, all of which were effective and successfully cured. Among them, 8 cases with no initial treatment were subsequently adjusted to doxycycline oral therapy + glucocorticoid therapy, and combined with fiberbronchoscopic alveolar lavage was selected according to the needs of the disease. All of them were clinically cured and discharged from hospital.

The effective rate of treatment was compared between groups by  $\chi^2$  test, and the  $P$  value  $> 0.05$  showed no statistical significance, so it could not be considered that the effective rate of the three methods was different (Table 1). The difference of effective groups under different treatment methods was analyzed statistically. Due to the ineffectiveness of early treatment, hospitalization days can be extended. The actual hospitalization days of MUMPP children in the three groups included in the analysis was longer than that of effective treatment due to inconsistent diagnosis time and inconsistent medication time nodes. Therefore, the adjusted hospitalization days was selected for comparison, and the days was the interval between effective treatment and clinical cure after diagnosis of MUMPP. Kruskal-Wallis test was used for comparison, and the adjusted hospitalization days in the three effective groups were  $P < 0.05$ , which showed a statistical difference. According to the rank sum test, the adjusted hospitalization days in groups A and B were  $P < 0.05$ , and there was a statistical difference. The adjusted hospitalization days in groups A and C were  $P < 0.05$ , and there was statistical difference. There was no statistical difference between group B and C in the adjusted hospitalization days ( $P > 0.05$ ). In addition, the average adjusted hospital stay of group B and C was shorter than that of group A, so it can be considered that the choice of doxycycline oral therapy can shorten the hospital stay of MUMPP children. See Table 2 and Table 3. Effective thermal regression time of each effective group: the difference between effective treatment and normal body temperature was selected for comparison. All children were given azithromycin orally before effective treatment, and the difference in the early stage time could affect the judgment of thermal regression time. Therefore, the difference between effective treatment and normal body temperature was calculated as the effective thermal regression time to determine whether there was a statistical difference.

Kruskal-Wallis test was used for comparison. Kruskal-Wallis test was used for comparison, and the effective thermal regression time among groups A, B and C showed no statistical difference ( $P > 0.05$ ). See Table 2. Lung imaging outcomes of all effective groups: All 44 MUMPP children underwent complete lung imaging examination (X-ray and chest CT) upon admission, 21 patients with large lung infection area or complicated lung consolidation were

re-examined before discharge, and no aggravation was found, and the remaining 23 patients were not re-examined. Before and after the comparison of imaging data, according to: 1 cure and 2 improvement statistics. The lung imaging data of 21 cases were included in the examination, and  $\chi^2$  test was used to compare the lung imaging outcomes among groups A, B and C,  $P > 0.05$ , and there was no statistical difference. See Table 2.

**Table 1.** Comparison of effective rates of different treatment methods for children with MUMPP.

Treatment methods	Effect		Total	P value
	Invalid	Valid		
Azithromycin + glucocorticoids	4	18	22	0.478
Doxycycline	4	19	23	
Doxycycline + glucocorticoids	0	7	7	
Total	8	44	52	

**Table 2.** Comparison of adjusted hospitalization days, effective fever recovery time, and imaging follow-up in different treatment methods and effective groups.

			Adjusted hospitalization days	Effective fever recovery time (days)	Imaging review	
					Healing (%)	Improvement (%)
Group	A	18	7 (5.75,8)	0 (0,0.25)	4 (33.3)	8 (66.7)
	B	19	5 (4,6)	1 (0,1)	2 (28.6)	5 (71.4)
	C	7	4 (3,6)	0 (0,0)	0 (0)	2 (100)
P value			0.01	0.116	0.627	

**Table 3.** Pairwise comparison of three groups of adjusted hospitalization days.

Comparison between groups	P value
A zithromycin + glucocorticoids	B Doxycycline
A zithromycin + glucocorticoids	C Doxycycline + glucocorticoids
B Doxycycline	C Doxycycline + glucocorticoids
	0.024
	0.009
	0.199

## 4. Discussion

MPP is a common respiratory disease in children, and macrolide therapy is a commonly used treatment method. With the increasing use of macrolide antibiotics, some children may experience drug unresponsiveness. Even with the rational use of macrolide antibiotics, the disease will still progress, often resulting in large consolidation shadows and pleural effusion in the lungs in a short period of time. In severe cases, it may be accompanied by respiratory distress syndrome, systemic inflammatory response syndrome, or damage to external organs, and even life-threatening [5]. MP infection has a periodic epidemic trend. Repeated or prolonged use of macrolide drugs is prone to MP resistance, and the resistance rate is increasing year by year [6], which may be one of the main reasons for the occurrence of MUMPP, SMPP, and RMPP. Resistance mechanisms of *Mycoplasma pneumoniae* are mainly related to changes in the targets of macrolide antibiotic action [7-9]. *Vivo* studies have found that macrolide resistance-associated mutations can be identified in 100% of patients after initiation of prolonged macrolide therapy [10]. *Vitro* studies have shown that subinhibitory concentrations of macrolides can induce resistance mutations [11]. The research results showed that the resistance rate of MP from 2016 to 2019 was 90.94% [6, 12]. Macrolide resistance may be an aggravating factor in the clinical manifestations of *Mycoplasma pneumoniae*

pneumonia [13]. Therefore, early identification of macrolide drugs and early intervention can promote better prognosis and reduce the occurrence of pulmonary and extrapulmonary complications and sequelae. In recent years, extensive research has been conducted both domestically and internationally on the treatment methods for refractory MPP (RMPP). Some studies have found that changing the type, dosage, administration method, and combination therapy of drugs may improve the efficacy [4]. Studying the differences in therapeutic effects of different treatment methods on such patients has practical significance for guiding clinical treatment, shortening treatment time for patients, and improving efficacy.

Macrolide drugs are the preferred drugs for children with MPP. Azithromycin is often taken orally in the treatment of children, and in severe cases, azithromycin can be administered intravenously. After 72 hours of treatment with macrolide antibiotics, the drug efficacy was preliminarily evaluated based on body temperature and other factors. At present, although macrolide resistance is considered in clinical practice, the detected resistance status and clinical efficacy are not entirely consistent. Clinical outcomes may also be related to the immune regulatory effect of macrolide drugs and factors related to disease course limitation. The data of this study shows that out of 52 children with MUMPP, 22 chose sequential oral treatment with azithromycin and intravenous corticosteroids. After treatment, 18 cases were successfully cured, and 4 cases were switched to other

treatments. It can be inferred that even if there is poor response of MP to macrolides, the combination of corticosteroids can still achieve clinical cure. This study compared the effectiveness of three groups and found that there was no significant difference in the treatment effectiveness between the azithromycin + glucocorticoid effective group and the doxycycline, doxycycline + glucocorticoid effective group in the treatment of MUMPP. This confirmed the effectiveness of azithromycin + glucocorticoid treatment for MUMPP.

Doxycycline belongs to the new tetracycline class of antibiotics and is an alternative drug for the treatment of *Mycoplasma pneumoniae* pneumonia. It has a definite therapeutic effect on drug-resistant *Mycoplasma pneumoniae* pneumonia and is used for the treatment of MUMPP, RMPP, SMPP that can or can be determined to be resistant to MP [14]. Due to the possibility of yellowing teeth and underdeveloped enamel, it is only suitable for children aged 8 and above. Children under the age of 8 who use medication beyond the instruction manual need to fully evaluate the pros and cons and obtain informed consent from parents. Doxycycline has high safety, and there have been no reports of persistent tooth yellowing or enamel hypoplasia within the recommended dosage and course of treatment [15]. At present, there is little experience in using doxycycline in children under 8 years old. Previous study treated 13 children with doxycycline intravenously and followed up on their adverse reactions during surgical treatment, but no tetracycline teeth were observed [16]. In this study, there were a total of 11 children under 8 years old who received oral doxycycline in the B and C effective groups, and 3 in the D initial ineffective group, all of which did not show tetracycline teeth. Several reports have shown clinical benefits of tetracyclines in terms of reduced symptom duration and rapid fever reduction [13]. In this study, the use of doxycycline reduced the effective length of hospitalization, providing a basis for these conclusions.

Glucocorticoids play an important role in the treatment of MUMPP. The degree of lung injury in MP infection may be related to the degree of immune response. Therefore, early treatment with glucocorticoids is essential to minimize the inflammatory response in MMP [17]. Some studies have shown that glucocorticoids can significantly reduce excessive immunity in inhibition, alleviate inflammatory reactions, and limit cytokine storms [18]. In the treatment of unresponsive *Mycoplasma pneumoniae* pneumonia in children with macrolides, they have a significant help in reducing body temperature and improving clinical symptoms. Reports from Korea have shown that glucocorticoids reduce disease incidence and decrease disease progression in RMPP and SMPP [19]. In this retrospective study, in the azithromycin + glucocorticoid treatment group and the doxycycline + glucocorticoid treatment group, the body temperature of children returned to normal after 0-3 days of hormone use. When the body temperature is normal, the symptoms improve, and CRP significantly decreases, it can gradually decrease and stop. The total course of treatment generally

does not exceed 14 days. When using, it is necessary to consider the side effects and adverse reactions of glucocorticoids and make corresponding measures.

## 5. Conclusion

A total of 52 children with MUMPP were included in this retrospective analysis, and different treatment methods were selected. It was found that azithromycin + glucocorticoid, doxycycline, doxycycline + glucocorticoid treatment can achieve clinical cure, and there was no significant statistical difference in treatment effectiveness. Classify and analyze the 44 effective treatment groups, and find that there are differences in age between each group, which can affect the choice of treatment methods, but does not affect the adjusted hospitalization days; There is no difference in gender, pneumonia type, and fever course among each group, and it can be considered that the severity of pneumonia in each group is similar, and the general information between each group is the same. On this basis, the adjusted hospitalization days of the doxycycline oral or doxycycline oral + glucocorticoid treatment group is shorter than that of the azithromycin sequential oral + glucocorticoid treatment group, which can shorten the hospitalization days to a certain extent.

This study addresses the efficacy comparison of treatment modalities for MUMPP. It demonstrates the superiority of choosing doxycycline treatment in MMP with poor treatment outcomes. We suggest that doxycycline and glucocorticoids may be considered when patients still have fever or worsening of chest imaging after 48-72 hours treatment with macrolide. However, the small sample size may raise inaccurate inferences, and more similar studies on the treatment of *mycoplasma pneumoniae* are needed. In addition, frequent use of antibiotics is often accompanied by the development of drug-resistant pathogens, and there remains a clinical need for safer and more effective treatments without concern.

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