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2026 Volume 11, Issue 2
Journal of Medicines Development Sciences
ISSN: 2382-6371 (Online)
ISSN: 2382-6363 (Print)

Comparison of the Efficacy of Two Initial Treatment Regimens for Macrolide-Unresponsive Mycoplasma Pneumoniae Pneumonia in Children

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Abstract: *Objective:* To compare the clinical efficacy of two first-line regimens—azithromycin combined with methylprednisolone versus doxycycline monotherapy—in the treatment of macrolide-unresponsive Mycoplasma pneumoniae pneumonia (MUMPP) in children. *Methods:* A retrospective study design was adopted. Children with MUMPP hospitalized in our institution from January 2023 to December 2023 were enrolled and divided according to their initial treatment regimen into Group A (azithromycin + methylprednisolone) and Group B (doxycycline monotherapy). Only cases that achieved clinical cure following the initial regimen were included in the between-group comparative analysis. The adjusted length of hospital stay required for clinical cure, time to effective defervescence, and pulmonary imaging resolution were compared between the two groups. Between-group comparisons were performed using the chi-squared test and the Mann–Whitney U test. *Results:* A total of 79 children with MUMPP who responded to treatment and met the discharge criteria for clinical cure were included, comprising 39 in Group A and 40 in Group B. No statistically significant difference in pulmonary imaging findings at discharge was observed between the two groups (P>0.05). The adjusted length of hospital stay was significantly shorter in Group B than in Group A (5 (IQR, 4–6) days vs. 7 (IQR, 6–9) days, p = 0.005). The time to effective defervescence did not differ significantly between the two groups. No serious adverse events occurred in either group. *Conclusion:* In children with MUMPP who respond to initial treatment, azithromycin combined with methylprednisolone and doxycycline monotherapy demonstrate comparable efficacy in terms of time to defervescence and final pulmonary imaging resolution; however, doxycycline significantly shortens the length of hospital stay required to achieve clinical cure.

Keywords: Children; Macrolide-unresponsive Mycoplasma pneumoniae pneumonia; Doxycycline; Azithromycin; Methylprednisolone

Online publication: June 23, 2026

1. Introduction

Mycoplasma pneumoniae (MP) is a common pathogen responsible for community-acquired pneumonia in children and adolescents[1], accounting for 10%–40% of pediatric pneumonia hospitalizations [2-3]. Published data indicate that the MP positivity rate in respiratory tract specimens from children reaches as high as 30.2%, with a particularly prominent proportion of infections among preschool-aged children [4]. In a study of children hospitalized with acute lower respiratory

tract infections, targeted next-generation sequencing (tNGS) revealed that MP infection accounted for 56.9% of pathogen-positive cases [5]. Concurrently, the incidence of severe Mycoplasma pneumoniae pneumonia in children has also demonstrated a year-on-year increasing trend [6].

Currently, macrolide antibiotics remain the first-line therapeutic choice for pediatric MPP [5,7]. However, with the widespread clinical use of these agents, drug-resistant strains have been increasingly identified. Some children show no significant clinical improvement, or even experience progressive deterioration, within 72 hours of initiating standard azithromycin treatment. To address this clinical challenge, the Chinese National Health Commission formally introduced the diagnostic concept of "macrolide-unresponsive Mycoplasma pneumoniae pneumonia" (MUMPP) in the 2023 Guidelines for the Diagnosis and Treatment of Mycoplasma pneumoniae Pneumonia in Children [8], aiming to assist clinicians in the early identification of high-risk children and to prevent progression to refractory or severe pneumonia.

When managing MUMPP, a common clinical dilemma is whether to continue with azithromycin-based therapy in combination with methylprednisolone or to switch directly to doxycycline. To date, data directly comparing the efficacy of these two first-line regimens remain limited. The present study retrospectively analyzed children with MUMPP admitted throughout 2023 who achieved clinical cure following their initial regimen, with the aim of systematically comparing the clinical outcomes of these two mainstream initial treatment strategies and providing evidence to guide first-line clinical decision-making.

2. Subjects and Methods

2.1. Study Subjects

This study is a retrospective case analysis,which was approved by the Medical Ethics Committee of Jingzhou First People's Hospital (Approval No.: KY2024-070-01). Children with MUMPP who were hospitalized in the Department of Pediatrics, Jingzhou First People's Hospital (The First Affiliated Hospital of Yangtze University) between January 2023 and December 2023, and who achieved clinical cure following their initial treatment regimen were enrolled. In this study, clinical cure was defined as: normalization of body temperature, stable vital signs, improved oxygenation status, ability to take oral medication with adequate intake maintained, absence of new or progressive complications, and sustained stability of the above status for more than three days [9].

Diagnostic criteria: In accordance with the 2023 Guidelines for the Diagnosis and Treatment of Mycoplasma pneumoniae Pneumonia in Children [8]: ① Confirmed diagnosis of Mycoplasma pneumoniae pneumonia; ② Persistent fever after 72 hours of standard macrolide antibiotic treatment, with no improvement or a progressive worsening trend in clinical symptoms and/or pulmonary imaging findings.

Inclusion criteria: Meeting the above diagnostic criteria; informed consent for special treatment with glucocorticoids and doxycycline (applicable to children under 8 years of age) signed by the child's guardian; an initial inpatient treatment regimen consisting of oral azithromycin plus intravenous methylprednisolone, or oral doxycycline monotherapy; effectiveness of the initial treatment regimen, with discharge after achieving the aforementioned clinical cure criteria.

Exclusion criteria: Co-infection with other confirmed bacterial or viral pathogens; concomitant acute exacerbation of bronchial asthma; children who required regimen change due to failure of the initial treatment; and those whose length of hospital stay was significantly prolonged due to non-pneumonia complications. Of particular note, during the study period, all children who failed initial treatment in either Group A or Group B were uniformly switched to a second-line regimen (doxycycline combined with methylprednisolone), with some receiving adjunctive fiberoptic bronchoscopic bronchoalveolar lavage, and were therefore excluded. Consequently, this study focuses on the specific population that responded to initial treatment, aiming to compare the difference in recovery speed between the two regimens in this population.

2.2. Treatment Regimens and Grouping

All children received routine symptomatic and supportive care after admission (including oxygen therapy, nebulized inhalation, expectorant use, and antipyretics when necessary). Based on the specific antimicrobial and anti-inflammatory strategies adopted, children were divided into two groups according to the initial clinical decision of the treating physician:

Group A (initial azithromycin + methylprednisolone): Azithromycin (Pfizer) was administered orally via sequential dosing based on body weight (10 mg/kg/day for those ≤25 kg, 0.25 g/day for those >25 kg; 5 days on, 3 days off, followed by another 3 days on and 4 days off), combined with intravenous methylprednisolone sodium succinate (1 mg/kg/dose, twice daily). The duration of methylprednisolone treatment was 3–7 days.

Group B (initial doxycycline monotherapy): Doxycycline hyclate tablets (Jiangsu Lianhuan Pharmaceutical) were administered orally at 2 mg/kg/dose every 12 hours for 10 consecutive days.

2.3. Outcome Measures

① Clinical cure: Achievement of the aforementioned clinical cure criteria, permitting hospital discharge.

② Adjusted length of hospital stay: The length of hospital stay from initiation of the current regimen to discharge.

③ Time to effective defervescence: The time interval (in days) from initiation of the current regimen to normalization of body temperature (sustained for more than 24 hours).

④ Pulmonary imaging resolution: Chest X-ray or CT was re-examined before discharge, and lesions were categorized as “complete resolution,” “majority absorption (≥50%),” “partial absorption (<50%),” and “progression.”

⑤ Drug safety: Drug-related adverse reactions during the treatment period were observed and recorded.

2.4. Statistical Methods

SPSS 27.0 software was used for data processing. Non-normally distributed continuous data were expressed as median (interquartile range) [M (P25, P75)]. Between-group comparisons were performed using the Mann–Whitney U test. Categorical data were compared between groups using the chi-squared test. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. General Data and Baseline Characteristics

A total of 79 children with MUMPP who achieved clinical cure following their initial regimen were enrolled in this study, including 39 in Group A and 40 in Group B.

No statistically significant differences were observed between the two groups in terms of sex distribution, duration of fever prior to admission, and pulmonary imaging classification at admission (P > 0.05), indicating good comparability between the two groups at enrollment. A statistically significant difference in age was noted between the two groups (P = 0.028), with Group B patients being slightly older than those in Group A, which is consistent with the clinical practice of more widespread doxycycline use in children over 8 years of age. This difference was addressed through subsequent subgroup analysis to exclude its potential confounding effect on the primary conclusions. Detailed baseline data are presented in **Table 1**.

Table 1. Comparison of baseline characteristics between the two groups

Baseline characteristic	Group A (n = 39)	Group B (n = 40)	Statistic	*P*-value
Male/Female (n)	24 / 15	25 / 15	$\chi^2 = 0.24$	0.624
Age (years, $\bar{x}\pm s$)	6.8 ± 2.5	7.6 ± 3.0	U = 612	0.028
Duration of fever before admission [M (P25, P75), days]	5 (4, 7)	5 (4, 6)	Z = −0.31	0.756
Imaging type at admission (lobar/non-lobar)	20 / 19	19 / 21	$\chi^2 = 0.18$	0.671

Note: Group A: azithromycin + methylprednisolone; Group B: doxycycline monotherapy.

3.2. Comparison of Core Clinical Outcomes

With respect to the adjusted length of hospital stay, Group B had a significantly shorter duration than Group A, with the difference reaching high statistical significance ($P = 0.005$), suggesting that doxycycline monotherapy can effectively shorten the time required to achieve clinical cure.

No statistically significant difference was observed in the time to effective defervescence between the two groups ($P > 0.05$), indicating that the two regimens are comparable in terms of the speed of temperature control. Detailed data are presented in **Table 2**. Notably, body temperature normalized within 48 hours after initiating the new regimen in children in both groups; cases with persistent fever beyond this time window were classified as initial treatment failure and were excluded from this analysis.

Table 2. Comparison of core clinical outcomes between the two groups

Indicator	Group A (n = 39)	Group B (n = 40)	*Z* value	*P*-value
Adjusted length of hospital stay [M (P25, P75), days]	7 (6, 9)	5 (4, 6)	−2.78	0.005
Time to effective defervescence [M (P25, P75), days]	1 (0, 1)	1 (0, 1)	−0.75	0.453

Note: Group A: azithromycin + methylprednisolone; Group B: doxycycline monotherapy.

3.3. Detailed Stratified Comparison of Pulmonary Imaging Resolution

A detailed stratified analysis of imaging resolution was conducted among children who completed follow-up imaging before discharge (19 in Group A and 20 in Group B). No statistically significant difference was observed in the distribution of imaging resolution between the two groups ($P = 0.977$). The vast majority of children in both groups achieved significant or complete absorption before discharge, with only a very small number (one case in each group) showing insignificant absorption or slight progression, suggesting that both regimens are highly effective in promoting the resolution of pulmonary lesions. Detailed data are presented in **Table 3**.

Table 3. Detailed stratification of imaging resolution at discharge in the two groups

Imaging resolution grade	Group A (n = 19)	Group B (n = 20)	Statistic
Complete resolution (cured)	6 (31.6%)	5 (25.0%)	$\chi^2 = 0.035$ $P = 0.977$
Significant absorption (≥50%)	10 (52.6%)	12 (60.0%)	
Partial absorption (<50%)	2 (10.5%)	2 (10.0%)	
Progression	1 (5.3%)	1 (5.0%)	
Total	19 (100%)	20 (100%)	

Note: Comparison of the distribution of imaging resolution between the two groups, $\chi^2 = 0.035$, P = 0.977.

3.4. Subgroup Analysis of Age on Adjusted Length of Hospital Stay

To further verify whether the difference in age between the two groups confounded the core findings, a subgroup analysis

stratified by age (< 8 years and ≥ 8 years) was performed. The results showed that in both the < 8 years and ≥ 8 years subgroups, the adjusted length of hospital stay in Group B was significantly shorter than that in Group A ($P < 0.05$ for both), indicating that the advantage of doxycycline monotherapy in shortening the length of hospital stay is independent of age. Detailed data are presented in **Table 4**.

Table 4. Subgroup analysis of age stratification and adjusted length of hospital stay

Age stratum	Group A Adjusted length of stay [M (P25, P75), days]	Group B Adjusted length of stay [M (P25, P75), days]	*Z* value	*P*-value
< 8 years (Group A: 24, Group B: 19)	7 (6, 9)	5 (4, 6)	Z = −2.36	0.018
≥ 8 years (Group A: 15, Group B: 21)	7 (6, 8.5)	5 (4, 6)	Z = −2.11	0.035

Note: Mann–Whitney U test was used for between-group comparisons in both subgroups.

3.5. Drug Safety Observations

During the study period, three children in Group A experienced transient hyperglycemia possibly related to methylprednisolone, and one child exhibited excitability and irritability, all of which resolved after symptomatic management. In Group B, two children developed mild nausea and abdominal discomfort, both of which were tolerable and did not interfere with continued medication. It is worth emphasizing that among all children under 8 years of age who received doxycycline treatment, no adverse reactions such as tooth discoloration were observed during hospitalization. No cases of treatment discontinuation due to adverse drug reactions occurred in either group.

4. Discussion

Macrolide resistance, particularly that mediated by the 23S rRNA A2063G/A2064G mutations, is the key factor contributing to the development of MUMPP in children [7,10]. In the face of this resistance dilemma, clinicians are often confronted with the choice between two initial treatment pathways: continuing azithromycin-based therapy in combination with methylprednisolone, or switching directly to doxycycline [7]. The present study focused specifically on the population of "initial treatment responders" and, through a retrospective analysis of 79 children with MUMPP who achieved clinical cure following their initial regimen, directly compared the clinical recovery speed of these two first-line regimens.

4.1. The Two Regimens Demonstrate Comparable Efficacy in Defervescence and Imaging Resolution

In this study, under the premise of effective initial treatment, both Group A and Group B demonstrated rapid defervescence, with no statistically significant difference in the time to effective defervescence between the two groups. This can be attributed to the distinct mechanisms of action of the two regimens: in Group A, methylprednisolone potently suppresses the excessive inflammatory response induced by MP infection, thereby rapidly controlling body temperature [7]; whereas in Group B, doxycycline directly eradicates the drug-resistant pathogen, blocking fever at its source. With regard to pulmonary imaging resolution at discharge, the proportion of children achieving significant lesion absorption exceeded 80% in both groups, with no statistically significant difference ($P = 0.977$). This indicates that, provided the initial treatment is effective, both regimens are capable of effectively controlling the progression of pulmonary lesions and promoting their resolution.

4.2. Doxycycline Demonstrates a Significant Advantage in Shortening Length of Hospital Stay

Although the speed of defervescence and imaging resolution were similar between the two groups, a notable difference was observed in the length of hospital stay required to achieve clinical cure. This study found that the median adjusted length of hospital stay in Group B (doxycycline monotherapy, 5 days) was significantly shorter than that in Group A (7

days). This finding suggests that, for susceptible MUMPP, antimicrobial therapy that directly targets the drug-resistant pathogen (doxycycline) may enable children to meet discharge criteria more rapidly than a combination regimen that suppresses downstream inflammation while leaving the drug-resistant pathogen in place. Furthermore, this difference may also be attributable to the fact that Group A required longer in-hospital observation due to intravenous methylprednisolone administration, whereas the entirely oral regimen in Group B was more efficient with respect to discharge decision-making. Through age-stratified analysis, we confirmed that this advantage is independent of the confounding effect of age, underscoring the robustness of the conclusion.

4.3. Value and Limitations of This Study

By strictly focusing on the population of "initial treatment responders," this study clearly addresses the clinically relevant question of "if the regimen is effective, which one leads to faster recovery," thereby providing evidence to inform the optimization of inpatient management. Furthermore, the preliminary safety observations support the notion that the short-term risks of both regimens are manageable. However, this study also has several limitations. First, as a single-center retrospective analysis with a limited sample size, the generalizability of the findings should be approached with caution; in particular, the overall treatment success rates of the two regimens cannot be compared on this basis. Second, approximately half of the children did not undergo follow-up imaging before discharge, which may have affected the completeness of the imaging evaluation to some extent. Large-sample, multicenter prospective studies that enroll the full spectrum of initially treated patients are warranted in the future to comprehensively evaluate the overall efficacy and safety of these two regimens.

5. Conclusion

Azithromycin combined with methylprednisolone and doxycycline monotherapy, as two initial treatment regimens for pediatric MUMPP, demonstrate comparable efficacy in terms of defervescence and pulmonary imaging resolution. However, doxycycline monotherapy can shorten the length of hospital stay required to achieve clinical cure. Under the premise of effective initial treatment, doxycycline monotherapy represents a therapeutic option capable of shortening the disease course and offering clinical advantages.

Disclosure statement

The author declares no conflict of interest.

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