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# Comparison of inflammatory control and safety by timing of doxycycline-azithromycin dual therapy in pediatric mycoplasmal pneumonia

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**Abstract**: The therapeutic approach of combining doxycycline (DOX) with azithromycin (AZM) has emerged as an effective strategy for managing pediatric Mycoplasmal pneumonia (MP), with its clinical efficacy well-established. It is worth noting that both DOX and AZM are antibiotics and require an interval of 24-72 hours when used in combination, but there are few studies on the optimal interval between the two drugs. This study aimed to elucidate the differential outcomes of two treatment regimens. The short-term group received DOX in combination with AZM within 24-72 hours after AZM administration for MP treatment, while the long-term group initiated DOX therapy more than 72 hours after AZM treatment. Our findings indicated that there were no statistically significant differences in clinical efficacy and the impact on pediatric pulmonary function between the two groups ($P>0.05$). However, the time for symptom improvement in the short-term group was significantly shortened ($P<0.05$), while the long-term group exhibited lower inflammatory responses, stress responses and a reduced incidence of complications ($P<0.05$). In conclusion, initiating DOX within 72 hours after AZM treatment can expedite the treatment course of MP, while using DOX more than 72 hours after AZM treatment confers enhanced safety.

**Keywords**: Azithromycin; Doxycycline; Inflammatory factors; Lung function; Mycoplasmal pneumonia; Stress response

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## INTRODUCTION

Epidemiological evidence identifies smokers, infants and immunocompromised populations as being particularly predisposed to Mycoplasmal pneumonia (MP) (Ding *et al.*, 2024). A study by Todkill D *et al*. has revealed that, since November 2023, the incidence of MP among children in England has been experiencing a sustained upward trend (Todkill *et al.*, 2024). Similarly, in China, pediatric MP has long been a serious medical concern. Over the past decade, reports have indicated a consistent increase in the incidence of MP in the Chinese population (Luo *et al.*, 2023). Notwithstanding the fact that the majority of MP cases are self-limiting with a favorable prognosis, approximately 10% of cases, due to the development of macrolide resistance (MR), progress to severe or refractory MP (Viteri-Davila *et al.*, 2024). Hence, the clinical management of these patients demands meticulous attention and appropriate therapeutic intervention.

Doxycycline (DOX), an excellent broad-spectrum antibiotic tetracycline, is widely used in the treatment of various infectious diseases or immunological dysfunctions, such as chronic obstructive pulmonary disease (Allinson *et al.*, 2023) and trachoma (Apato *et al.*, 2024). Regarding MP, emerging research has preliminarily validated that the combination of DOX and azithromycin (AZM) represents an efficacious treatment strategy, with its therapeutic benefits corroborated through multiple investigations (Song *et al.*, 2024; Lee *et al.*, 2021). Nonetheless, given that both agents are antibiotics, concurrent use may potentially interfere with each other's pharmacodynamics (Greco Kinney *et al.*, 2023). Consequently, in clinical practice involving combination therapies, a dosing interval of 24-72 hours between DOX and AZM is typically recommended. At present, however, there is a paucity of reliable clinical guidance regarding the optimal selection of this dosing interval. Recently, a study conducted by Chen Y *et al*. demonstrated that pediatric MP patients who received DOX within three days following AZM treatment exhibited a reduction in both fever duration and hospital length of stay (Chen *et al.*, 2024), providing novel insights for the clinical application of DOX. Nevertheless, their study failed to comprehensively explore the implications of varying DOX administration timings on such patients. Additionally, the relatively limited sample size (comprising only 58 subjects in the study by Chen Y *et al*.) introduces a significant element of randomness.

Therefore, this study aims to comprehensively compare the impacts of different DOX administration timings on pediatric MP patients. The findings are expected to provide more reliable guidance for future clinical treatment of MP and improve the prognosis of these patients.

## MATERIALS AND METHODS

### *Research design*

A retrospective analysis was designed, with the target population including pediatric MP patients admitted to our

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hospital between January 2023 and August 2024. To determine the appropriate sample size, the G*Power software was employed. The parameters were configured as follows: two-tailed test (Tail), an effect size of 0.3, an α err prob of 0.05, a Power of 0.95, considering a 20% dropout risk, at least 160 cases of research subjects.

***Research subjects***

After screening according to the inclusion and exclusion criteria, 197 pediatric patients diagnosed with MP and treated in our hospital were selected as the study subjects. 93 patients who added DOX therapy within 24-72 hours after AZM treatment were considered the short-term group. The remaining 104 patients, who used DOX treatment more than 72 hours after AZM administration, were set as the long-term group. Inclusion criteria: Confirmed diagnosis of MP through examination; Age ranging from 8 to 15 years old; Complete medical records and use of AZM and DOX combination therapy after admission. Exclusion criteria: Children with mixed infections; Those with pre-existing chronic conditions predisposing them to pulmonary infections, such as pulmonary tuberculosis, asthma and immunodeficiency; Children with congenital heart diseases; Patients with drug allergies; Children who had received any antibiotic therapy within 2 weeks before admission.

***Methods***

Upon admission, all pediatric patients were administered AZM (manufactured by Guangzhou Baisailuo Pharmaceutical Co., Ltd., Approval Number H20073845) at a dosage of 10 mg/kg per day for one week. In the short-term group, DOX (produced by Kaifeng Pharmaceutical Co., Ltd., Approval Number H41020946) was concurrently prescribed within the first three days following the initiation of AZM treatment. The dosage of DOX was 2 mg/kg, administered twice daily for one week. In contrast, the long-term group received DOX in combination with AZM three days after the start of AZM therapy, with the same dosage regimen as that of the short-term group.

***Efficacy evaluation***

*Cured*: After treatment, all the clinical symptoms were completely resolved. Computed tomography (CT) imaging demonstrated the complete disappearance of pulmonary lesions and mycoplasmal tests for diagnostic infections yielded negative results. *Markedly effective*: A significant improvement in symptoms was observed, accompanied by a reduction in pulmonary lesions by at least 90%. *Effective*: Clinical symptoms were effectively controlled; however, the reduction in pulmonary lesions was less than 90%, thereby necessitating the continuation of treatment. *Ineffective*: Cases that did not satisfy any of the above-mentioned criteria were deemed ineffective (Fan *et al.*, 2023). All CT images were read by two radiologists independently and a third radiologist was consulted when the results of two radiologists were inconsistent. All radiologists were unaware of the group assignments.

***Evaluation of pulmonary function, inflammatory reaction and stress response***

Before and after treatment, a pulmonary function tester was utilized to measure the maximal mid-expiratory flow (MMF), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF) and forced vital capacity (FVC). Additionally, fasting venous blood samples were collected from the pediatric patients before (children were admitted within 2h after admission prior to any treatment) and after treatment (2 hours after completion of all treatments). The levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and lipid peroxide (LPO) were determined via the ELISA method. Hypersensitive-C reactive protein (hs-CRP), albumin (ALB) and total bilirubin (TBIL) were measured using an automatic biochemical analyzer.

***Endpoints***

(1) Clinical efficacy was assessed. (2) The time of cough resolution, body temperature normalization and lung rales disappearance was recorded (symptom resolution times recorded by pediatricians during twice-daily ward rounds using standardized criteria. Cough cessation: ≥8 hours without coughing. Lung rales disappearance: Absence on auscultation by two clinicians. The time of body temperature normalization record for a child with normal body temperature is 0). (3) Changes in pulmonary function (FVC, PEF, MMF and FEV1), inflammatory factors (hs-CRP, IL-6 and TNF-α) and stress response (LPO, ALB and TBIL) before and after treatment were analyzed. (4) The incidence of complications during treatment was counted.

***Statistical analysis***

SPSS 25.0 was used for statistical analysis. For the comparison of categorical data presented as [n(%)], the Chi-square test was utilized. When dealing with measurement data following a normal distribution, expressed as ( $\bar{\chi} \pm s$), independent-sample t-tests and paired t-tests were employed for comparisons. Bonferroni correction applied for multiple comparisons ($\alpha=0.05/6=0.008$ for 6 inflammatory/stress markers). In all statistical tests, a significance level of $P<0.05$ was adopted.

## RESULTS

***Comparison of clinical data***

Given the retrospective analysis design, we first determined the comparability between the two groups of research subjects. Through a comprehensive comparison of parameters such as age, sex and disease course between the short-term group and the long-term group revealed no statistically significant differences between the two groups ($P>0.05$, Table 1).

***Comparison of clinical efficacy***

Statistics on clinical efficacy showed that the total effective rate was 94.62% in the short-term group and 93.27% in the

long-term group, with no difference between the two groups (P>0.05, Table 2).

***Comparison of symptom improvement***

In the short-term group, the time of cough resolution, body temperature normalization and lung rales disappearance were (5.87±1.03) d, (2.26±1.05) d and (8.00±1.99) d respectively. In comparison with the long-term group, the short-term group exhibited a significantly shorter time for symptom improvement (P<0.05, Table 3).

***Comparison of pulmonary function***

The two groups showed no notable differences in pulmonary function before and after treatment, (P>0.05). When compared to the pre-treatment values, post-treatment measurements of FVC, PEF, MMF and FEV1 in both groups showed a significant increase (P<0.05, Fig. 1).

***Comparison of inflammatory factors***

Prior to treatment, no significant differences were observed in the detection results of inflammatory factors between the two groups (P>0.05). After treatment, the levels of hs-CRP, IL-6 and TNF-α decreased in both groups (P<0.05). However, the levels in the short-term group were significantly higher than those in the long-term group (P<0.05, Fig. 2), indicating a more pronounced post-treatment inflammatory response in the short-term group.

***Comparison of stress response***

In the assessment of stress response, no differences were found in the levels of LPO, TBIL and ALB between the two groups before treatment (P>0.05). After treatment, LPO levels decreased in both groups, yet the level in the short-term group remained significantly higher (P<0.05). Conversely, TBIL levels increased, with the short-term group showing a significantly lower level compared to the long-term group (P<0.05). Additionally, ALB levels increased in both groups after treatment (P<0.05, Fig. 3). These findings suggest a higher stress response in the short-term group.

***Comparison of safety***

Finally, in the statistics of adverse reactions, the complication incidence rates in the short-term group and the long-term group were 25.86% and 14.89%, respectively. The short-term group had a significantly higher complication incidence rate (P<0.05, Table 4).

## DISCUSSION

Mycoplasmal pneumonia, being one of the major diseases that can significantly impact children's health and even pose threats to their life safety, necessitates substantial clinical emphasis regarding its treatment (Li *et al.*, 2024). In this study, we explored the dosing interval in the combined treatment of MP using DOX and AZM. First, with respect to clinical efficacy, a comparative analysis revealed no significant disparities in the overall treatment efficacy rate and pulmonary function parameters between the two groups. This further corroborates the remarkable therapeutic efficacy of DOX plus AZM therapy in the treatment of MP. AZM, belonging to the macrolide antibiotic family, exerts its anti-mycoplasma action through the inhibition of protein synthesis. Previous clinical evidence (Cheng *et al.*, 2024) has demonstrated that a majority of children diagnosed with MP respond favorably to AZM treatment.

However, in recent years, due to a decline in the sensitivity of mycoplasma to AZM, an increasing number of MP-infected children have been detected with resistant gene mutations such as A2063G, A2064G and A2017G, resulting in a reduction in the therapeutic efficacy of macrolides (Kim *et al.*, 2022). DOX, a member of the tetracycline-class antibiotics, exhibits a distinct antibacterial mechanism compared to AZM. Specifically, DOX exerts its action primarily on the 30S subunit of the pathogen's ribosome. By modulating the permeability of the cell membrane, DOX induces the leakage of nuclear components, including nucleotides. This, in turn, hinders the elongation of the peptide chain during protein synthesis and suppresses the synthesis of DNA in the lesion. Notably, in the human body, DOX is characterized by a relatively long half-life and a short duration of action, enabling it to effectively inhibit protein synthesis and thus eradicate bacteria (Chen *et al.*, 2022).

However, in the comparative analysis of the time taken for clinical symptom amelioration between the two groups of children, we found that the short-term group had a shorter duration for cough resolution, body temperature normalization and the disappearance of lung rales. This observation strongly indicates that the administration of DOX within 72 hours following AZM treatment contributes to a more expeditious improvement of symptoms associated with MP. Kabir KI *et al*. found that the fever remission rate within 72 hours of treating children with scrub typhus using either DOX or AZM alone was over 90% and when the two drugs were used in combination, the remission rate could reach approximately 100% (Kabir *et al.*, 2022).

The underlying mechanism can be attributed to the synergistic effect of DOX and AZM against diverse pathogens. When used in combination, these two drugs enhance the antibacterial efficacy, thereby enabling more rapid alleviation of MP symptoms. Additionally, the use of antibiotics from different classes can mitigate the emergence of drug resistance, thus providing a more robust guarantee for the therapeutic efficacy of MP treatment. Consequently, the pediatric patients in the short-term group, who received the two drugs in combination more promptly, experienced a shorter treatment cycle.

**Table 1**: There was no difference in the clinical data between the two groups

| | Short-term (n=93) | Long-term (n=104) | t or $\chi^2$ | P |
|---|---|---|---|---|
| Disease course (d) | 5.67±0.89 | 5.83±0.79 | 1.337 | 0.183 |
| Sex | | | 0.998 | 0.318 |
| Boys | 54 (58.06%) | 53 (50.96%) | | |
| Girls | 39 (41.94%) | 51 (49.04%) | | |
| Age | 10.98±2.37 | 11.37±2.19 | 1.189 | 0.236 |
| Weight (kg) | 30.30±2.83 | 30.82±3.22 | 1.190 | 0.236 |
| Fever* | | | 0.798 | 0.850 |
| Low fever (37.3-38°C) | 30 (32.26%) | 38 (36.54%) | | |
| Moderate fever (38.1-39°C) | 35 (37.63%) | 35 (33.65%) | | |
| High fever (>39°C) | 17 (18.28%) | 21 (20.19%) | | |
| Normal (≤37.2°C) | 11 (11.83) | 10 (9.62%) | | |
| Only child | | | 0.631 | 0.427 |
| Yes | 75 (80.65%) | 79 (75.96%) | | |
| No | 18 (19.35%) | 25 (24.04%) | | |
| Previously had MP | | | 0.931 | 0.335 |
| Yes | 12 (12.90%) | 9 (8.65%) | | |
| No | 81 (87.10%) | 95 (91.35%) | | |

Note: * fever is measured in the oral cavity.

**Table 2**: There was no difference in clinical outcomes between the two groups

| Group | Cured | Markedly effective | Effective | Ineffective | Total effective rate (Cured+Markedly effective+Effective) |
|---|---|---|---|---|---|
| Short-term (n=93) | 17 (18.28%) | 49 (52.69%) | 22 (23.66%) | 5 (5.38%) | 94.62% |
| Long-term (n=104) | 20 (19.23%) | 58 (55.77%) | 19 (18.27%) | 7 (6.73%) | 93.27% |
| t | | | | | 0.157 |
| P | | | | | 0.692 |

**Table 3**: The short-term group had a shorter recovery time

| Groups | Time of cough resolution (d) | Time of body temperature normalization (d)* | Time of lung rales disappearance (d) |
|---|---|---|---|
| Short-term (n=93) | 5.87±1.03 | 2.26±1.05 | 8.00±1.99 |
| Long-term (n=104) | 6.94±1.46 | 2.97±1.30 | 8.80±2.75 |
| t | 5.877 | 2.172 | 2.310 |
| P | <0.001 | 0.031 | 0.022 |

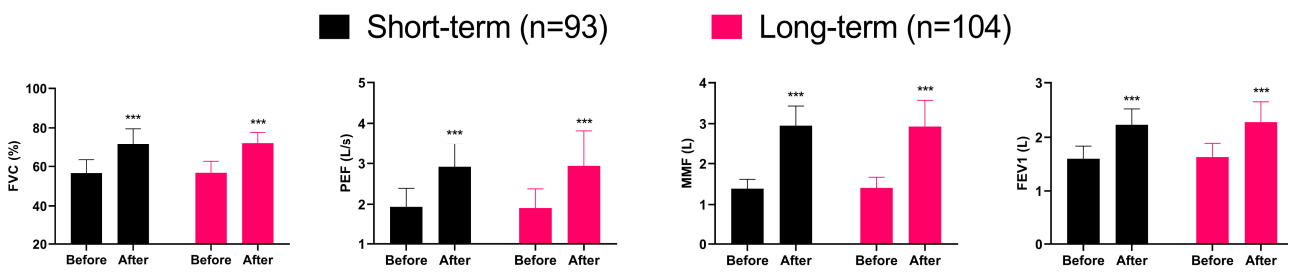


**Fig. 1**: Demonstrates the comparison of lung function between the two groups of children before and after treatment.
Note: *** indicates P<0.05 compared with before treatment.

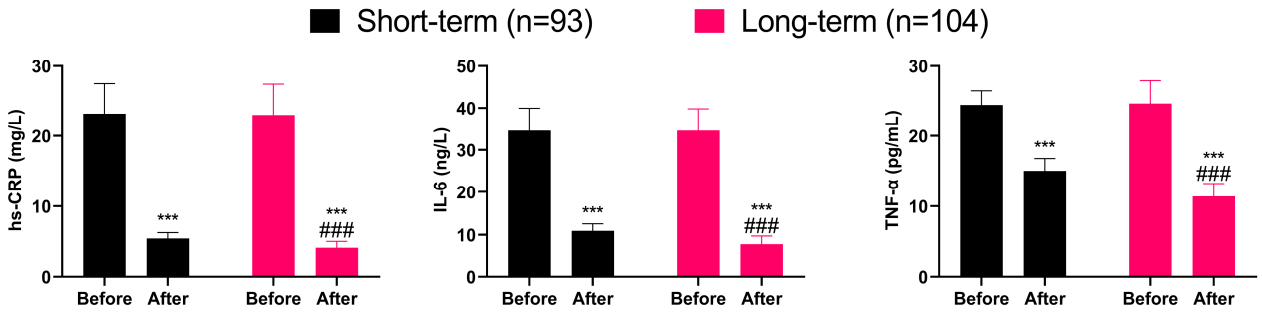


**Fig. 2**: Demonstrates the comparison of inflammatory factors between the two groups of children before and after treatment. Note: *** indicates P<0.05 compared with before treatment, ###indicates P<0.05 compared with short term group.

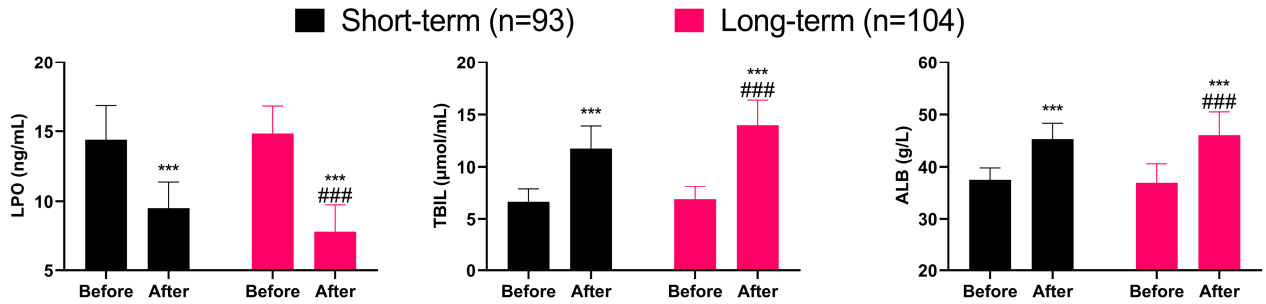


**Fig. 3**: Demonstrates the comparison of stress response between the two groups of children before and after treatment. Note: *** indicates P<0.05 compared with before treatment, ###indicates P<0.05 compared with short term group.

**Table 4**: The incidence of adverse reactions was higher in the short-term group

| Group | Vomiting | Abdominal pain or diarrhea | Rash | Tetracycline teeth | Allergies | Total incidence rate |
|---|---|---|---|---|---|---|
| Short-term (n=93) | 5 (5.38%) | 5 (5.38%) | 2 (2.15%) | 1 (1.08%) | 2 (2.15%) | 25.86% |
| Long-term (n=104) | 2 (1.92%) | 3 (2.88%) | 1 (0.96%) | 0 (0.0%) | 1 (0.96%) | 14.89% |
| $\chi^2$ | | | | | | 4.371 |
| P | | | | | | 0.037 |

Similarly, in a study by Lu Z *et al*. on the treatment of non-gonococcal urethritis, it was also found that the combination of DOX and AZM could lead to more rapid symptom relief in patients (Lu *et al.*, 2020).

However, we observed that compared with the long-term group, the short-term group exhibited significantly exacerbated inflammatory and stress responses, along with an increased incidence of complications. This suggests that a relatively short dosing interval between DOX and AZM may potentially elevate the medication-related risks for pediatric patients. The elevated inflammation in the short-term group persisted despite uniform sampling timing, suggesting biological differences rather than measurement artifacts. Transient inflammation may result from rapid bacterial lysis via synergistic antibiotic action. Although the safety of both DOX and AZM has been well-established and clinically validated (Xie *et al.*, 2022; Tsalik *et al.*, 2023), as members of the antibiotic class, they both carry potential cardiotoxicity. Their administration may predispose patients to an increased likelihood of experiencing gastrointestinal disturbances, allergic reactions and other adverse events. This is precisely why, in clinical practice, a dosing interval of 24-72 hours is required when the two drugs are used in combination. Notably, in a study by Greco Kinney A *et al*., it was posited that the combined use of DOX and AZM in the treatment of critically ill patients with community-acquired pneumonia did not increase the risk of developing malignancy (Greco Kinney *et al*., 2023), which is contrary to our findings. We postulate that this discrepancy may be attributable to the fact that the subjects in the study by Greco Kinney A *et al*. were exclusively adults aged 18 years or older, whereas our research cohort consisted solely of children. The differences in basic physical conditions may render children more prone to developing complications. Furthermore, DOX is derived from tetracycline by removing the hydroxyl group at the C-6 position. This molecular modification results in a reduction of DOX's calcium-binding capacity by half, thereby

potentially impeding the normal growth and development of dental structures in humans (Okic Dordevic *et al.*, 2023). In addition, pharmacokinetic interactions underlie the safety differences. AZM inhibits CYP3A4, increasing DOX bioavailability. Concurrent dosing saturates P-gp efflux transporters, prolonging GI exposure (Drozdzal *et al.*, 2020). Pediatric CYP3A4 activity is 30% lower than adults (Streekstra *et al.*, 2024), which explains the increased incidence of vomiting in the short-term group. Taking the results of this study together with those of previous studies, for pediatric populations, we recommend: (1) Routine dental monitoring for children receiving >3 treatment cycles; (2) Staggered dosing (≥4h) to minimize drug-drug interactions; (3) Proton-pump inhibitor prophylaxis in high-risk patients.

Meanwhile, given that this research is a single-center retrospective analysis, future investigations should consider including more cases and conducting randomized controlled trials to validate and further analyze the findings. Additionally, a long-term follow-up assessment of the pediatric subjects in this study is imperative, which can help us comprehensively evaluate the long-term prognostic implications of the DOX plus AZM therapy on MP.

## CONCLUSION

The combination of DOX and AZM demonstrates remarkable efficacy in the treatment of MP, effectively enhancing the pulmonary function of pediatric patients. Specifically, the administration of DOX within 72 hours after AZM treatment leads to a more expeditious improvement of clinical symptoms, thereby shortening the treatment duration. Conversely, initiating the combination of DOX with AZM more than 72 hours after AZM treatment confers a higher level of safety, as it mitigates both the inflammatory and stress responses in pediatric patients.

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***Author's contributions***
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***Data availability statement***
The data that support the findings of this study are available from the corresponding author upon reasonable request.

***Ethical approval***
The study has been approved by the Ethics Committee of Lixin County People's Hospital (No. KL2022041), and consent forms were signed by all participants' parents/guardians.

***Conflict of interest***
The authors report no conflict of interest.

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