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Clinical Efficacy of Azithromycin in the Treatment of Pediatric *Mycoplasma pneumoniae* Pneumonia and Its Impact on Platelet Count and D-Dimer Levels

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Objective: To analyze the clinical efficacy of azithromycin in the treatment of pediatric *Mycoplasma pneumoniae* pneumonia and its impact on platelet count and D-dimer levels.

Methods: A comparison was made between the two groups regarding clinical treatment effects, recovery status, levels of blood indicators [C-reactive protein (CRP), white blood cell count (WBC), platelet count (PLT), D-dimer (D-D)], and the occurrence of adverse reactions. The control group received conventional symptomatic treatment, while the case group received both conventional treatment and azithromycin.

Results: ① Clinical treatment effects: The total effective rate of treatment in the control group was 84.21%, while it was significantly higher at 96.83% in the case group ($P < 0.05$). ② Recovery status: After treatment, the case group exhibited significantly shorter durations for fever clearance, cough disappearance, rale disappearance, resolution of chest radiographic shadows, and hospital stay compared to the control group ($P < 0.05$). ③ Blood indicator levels: After treatment, the levels of C-reactive protein (CRP), white blood cell count (WBC), platelet count (PLT), and D-dimer (D-D) were significantly lower in the case group than in the control group, indicating an improvement in the inflammatory response and blood clotting status.

Conclusion: Addition of azithromycin to conventional symptomatic treatment significantly improves the efficacy of Mycoplasma pneumoniae pneumonia treatment in children, reduces inflammatory response, improves blood circulation, further promotes recovery without a substantial increase in related adverse reactions, suggesting its relatively high safety in clinical application and advocating for its clinical promotion.

Keywords: azithromycin, pediatric Mycoplasma pneumoniae pneumonia, clinical efficacy, platelet count, D-dimer

Introduction

Pediatric *Mycoplasma pneumoniae* pneumonia *(PMPP)* is a respiratory tract infection caused by Mycoplasma, primarily affecting infants, toddlers, and preschool-aged children. Its incidence has shown a rising trend.[1] Clinically, this condition typically presents respiratory symptoms such as coughing, wheezing, fever, and chest rales. Its course of progression is uncertain and at times may lead to severe complications like bronchitis, pneumonia, among others.[2] Mycoplasma infections hold a significant position in respiratory tract infections, posing several challenges in diagnosis and treatment. The virological diversity and variability of Mycoplasma have an impact on accurate diagnosis, particularly in cases where typical clinical symptoms are not evident.[3] In terms of treatment, conventional approaches primarily involve supportive symptomatic treatment, such as fever reduction and maintaining electrolyte balance. However, these methods often fail to completely halt the progression of the disease. Additionally, Mycoplasma infections can trigger inflammatory responses within the body and affect blood clotting functions, aspects that current treatments have not fully addressed. According to the World Health Organization (WHO), the standard treatment for PMPP typically categorized as follows. In cases of pneumonia characterized by "fast breathing", the standard treatment was oral cotrimoxazole. For children exhibiting "chest indrawing", referral to a healthcare facility was necessary, where they would receive injectable penicillin or ampicillin. However, emerging evidence

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prompted a significant revision in 2014, which favored oral amoxicillin as the first-line treatment for fast-breathing pneumonia. This change reflected findings that demonstrated oral amoxicillin's efficacy comparable to that of injectable penicillin or ampicillin for chest-indrawing pneumonia as well. Consequently, the classification system was streamlined to two primary categories: the first being "pneumonia", defined as fast breathing and/or chest indrawing, which can be effectively managed at home with oral amoxicillin. The second category, "severe pneumonia", includes pneumonia accompanied by any general danger signs, necessitating referral for injectable antibiotic treatment.[4]

Antibiotics rank among the most transformative medical breakthroughs of the 20th century, drastically reducing mortality from infectious diseases. However, the rise of antimicrobial resistance (AMR) has become a critical concern, driven by the extensive and often inappropriate use of these medications. AMR primarily spreads through human interactions, both in healthcare settings and the wider community. Numerous interconnected factors in healthcare and agriculture contribute to the evolution of AMR, utilizing various mechanisms of drug resistance. A significant factor in this rise is the unrestricted use of antimicrobials in livestock feed, which has accelerated the emergence and dissemination of resistant strains. The prevalence of antibiotic-resistant bacteria has reached alarming levels globally, posing a serious threat to public health and requiring immediate action. Treatment options for infections caused by these resistant organisms are increasingly limited, leading to higher rates of morbidity and mortality, as well as substantial economic burdens. The stark contrast between the urgent need for new antimicrobial agents and the slow pace of their discovery further exacerbates this crisis.[5]

In our hospital, azithromycin was introduced as a treatment option for several reasons. Notably, there has been an increasing incidence of antibiotic resistance among pathogens, including *Mycoplasma pneumoniae*. Studies have shown that certain strains have developed resistance to traditional antibiotics like erythromycin, necessitating the use of azithromycin, which has demonstrated superior efficacy and a better safety profile. At the time of this study, the antibiotic treatment regime in our hospital primarily involved erythromycin for Mycoplasma infections. However, due to observed cases of treatment failure and adverse effects associated with prolonged erythromycin use, we transitioned to incorporating azithromycin as a complementary treatment option. This shift aimed to enhance clinical outcomes by reducing recovery times and minimizing the inflammatory response associated with PMPP.

Azithromycin, as a broad-spectrum antibiotic, has been widely used in the treatment of respiratory tract infections. Its unique pharmacological effects include inhibiting bacterial protein synthesis and regulating immune inflammatory responses.[6] However, the precise mechanism of action of azithromycin in the treatment of PMPP remains incompletely understood.

Given the diagnostic and therapeutic challenges in current PMPP, this study retrospectively analyzes the efficacy of azithromycin in treating PMPP. It particularly focuses on its impact on physiological markers in children, such as platelet count and D-dimer levels. By comparing the differences in efficacy between the azithromycin case group (case group) and the conventional case group (control group), we aim to uncover the potential role of azithromycin in ameliorating symptoms, regulating inflammatory responses, and blood clotting status. This aims to provide a more comprehensive and effective strategy for treating PMPP. Additionally, we will explore the safety profile of azithromycin during treatment to evaluate its overall benefits as a therapeutic intervention. In this context, gaining a deeper understanding of the efficacy and safety of azithromycin holds significant importance in guiding clinical practices and offering a more scientifically grounded basis for the treatment of PMPP.

Objects and Methods

Study Subjects

A retrospective analysis was conducted on the clinical data of 120 pediatric patients diagnosed with Mycoplasma pneumoniae pneumonia in our hospital from February 2021 to November 2023. Inclusion criteria: ① Children diagnosed with *Mycoplasma pneumoniae* pneumonia through clinical tests, with positive Mycoplasma antibody detection;[4] ② Children aged <10 years, regardless of gender; ③ Children exhibiting varying degrees of high fever, coughing, and lung changes in X-rays indicative of pneumonia; ④ Duration of illness <14 days; ⑤ Clinical data of children being complete, authentic, and available for analysis. Exclusion criteria: ① Children with a history of chronic lung diseases or recurrent respiratory infections; ② Children with mixed infections of other pathogens; ③ Children who received recent (within 3 months) immune, anti-infection, or anti-inflammatory treatments; 4) Children allergic or with contraindications to

drugs or methods used in this study; 5) Children and family members with cognitive impairments, consciousness disorders, or related conditions. Based on the treatment interventions received, they were divided into a control group (n=57) and a case group (n=63). Children in the control group received conventional symptomatic treatment, while those in the case group received additional azithromycin treatment on top of the control group's treatment.

The protocol was approved by the ethics committee of Anhui Provincial Children's Hospital (2020981). Informed consent was obtained from the parents or legal guardians of the study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Methods

Control Group

Children in the control group received conventional symptomatic drug treatment, including cough suppressants, bronchodilators, expectorants, oxygen therapy, and a sequential therapy of *Oral doxycycline*. 200 mg on day 1, followed by 100 mg once daily for the following 6 days. After improvement in clinical symptoms, white blood cell counts were checked, and if restored to normal, a switch was made to oral roxithromycin tablets (SANOFI, Batch No.: 9NM8A), at 20 mg/(kg·d), twice daily. A course of treatment comprised continuous use for 7 days.

Case Group

Children in the case group received azithromycin in addition to the treatment provided to the control group. The initial symptomatic and erythromycin drug treatment methods in the case group were consistent with those in the control group. Azithromycin (Ankang Beiyi Pharmaceutical Co., Ltd., NMPA Approval No. H20073718) was administered as a sequential therapy at 10 mg/(kg·d) through intravenous infusion, once daily, with each administration lasting >2 hours. After improvement in clinical symptoms, white blood cell counts were checked, and if restored to normal, azithromycin powder for oral suspension (Pfizer Pharmaceuticals Limited, Batch No.: AW4935) was administered at 10 mg/(kg·d), once daily. A course of treatment involved continuous use for 3 days followed by a 4-day hiatus. Both groups of children received 1–3 courses of treatment based on improvement in clinical symptoms and signs.

Observation Indices

1. Clinical Treatment Effect: Cure: Children showed normal signs and symptoms, with no abnormalities in chest X-rays and laboratory tests after treatment. Marked Effect: Children showed significant improvement in signs and clinical symptoms after treatment, with evident improvement in chest X-rays and laboratory test results, but at least one aspect did not achieve satisfactory results. Effective: Children showed improvement in signs, symptoms, and test results after treatment, but did not reach normal levels. Ineffective: Children showed no significant changes or even worsening of signs, symptoms, and test results after treatment. Total Effective Rate = (Cure + Marked Effect + Effective) cases / Total cases × 100%.
2. Recovery Conditions: The recovery indices included in this study were: fever resolution time, cough disappearance time, wheezing disappearance time, disappearance time of chest X-ray shadows, and length of hospital stay, all of which were uniformly recorded by relevant medical staff in our hospital.
3. Blood Indicator Levels: After completion of the treatment, 5 mL of fasting morning cubital vein blood was collected from the children. Standard centrifugation was performed to obtain the serum. Enzyme-linked immunosorbent assay (ELISA) was utilized to measure the level of C-reactive protein (CRP) in the children's bodies. Immunoturbidimetric assay was employed to determine the white blood cell count (WBC) levels. An automated hematology analyzer was used to examine the platelet count (PLT) levels. Additionally, colloidal gold immunochromatography was applied to assess the serum D-dimer (D-D) levels in the children's bodies.
4. Occurrence of Adverse Reactions: Adverse reactions observed in this study included: dizziness, headache, nausea, vomiting, gastrointestinal reactions, skin reactions, hypoglycemia, etc. The occurrence of these adverse reactions was uniformly recorded by relevant medical staff in our hospital.

Statistical Analysis

SPSS 22.0 was employed for data analysis. For continuous data, the distribution was described using mean and standard deviation, and statistical analysis was conducted using the *t*-test method. For categorical data, distribution was described using frequency and percentages, and statistical analysis was performed using the chi-square test method. A significance level of P<0.05 was considered statistically significant.

Results

Baseline Data Comparison

The baseline characteristics of the two groups of patients were comparable, showing no significant differences in comparison (P > 0.05). Refer to Table 1 for details.

Comparison of Clinical Treatment Effects

The total effective rate of treatment was 84.21% in the control group and 96.83% in the case group, demonstrating a significantly higher total effective rate in the case group compared to the control group (P < 0.05). Refer to Table 2 for details.

Comparison of Recovery Progress

Following treatment, the case group exhibited significantly lower durations for fever resolution, cough disappearance, rale disappearance, disappearance of pulmonary shadow in X-ray, and hospital stay compared to the control group (P < 0.05). Refer to Table 3 for details.

Comparison of Blood Indicator Levels

Following treatment, the levels of CRP, WBC, PLT, and D-D in the case group were significantly lower than those in the control group (P<0.05). Refer to Table 4.

Table 1 Baseline Data Comparison

	Control (n=57)	Case (n=63)	t/χ^2	P
Gender			0.004	0.948
Male	32	35	–	–
Female	25	28	–	–
Age (years)	5.69±2.37	5.74±2.21	0.119	0.905
Duration (days)	9.26±1.34	9.37±1.25	0.465	0.642
Severity of Illness			0.224	0.635
Mild	22	27		
Moderate	35	36		
SBP (mmHg)	91.45±8.16	91.77±8.01	0.216	0.828
DBP (mmHg)	65.83±8.27	65.49±8.32	0.224	0.823
HR (beats/min)	102.04±7.98	101.85±8.06	0.129	0.897

Table 2 Comparison of Clinical Treatment Effects

Group	n	Cured	Markedly Effective	Effective	Ineffective	Total Effective Rate (%)
Control	57	14	19	15	9	84.21%
Case	63	20	27	14	2	96.83%
χ^2	–	–	–	–	–	5.719
P	–	–	–	–	–	0.016

Table 3 Comparison of Recovery Progress (Days)

Recovery Indicator	Control (n=57)	Case (n=63)	t	P
Fever Resolution Time (d)	3.85±1.16	2.17±1.32	7.372	<0.001
Cough Disappearance Time (d)	5.58±1.47	3.46±1.59	7.559	<0.001
Rale Disappearance Time (d)	6.83±1.59	4.83±1.27	7.646	<0.001
Pulmonary Shadow Disappearance Time (d)	6.94±1.77	4.27±1.39	9.233	<0.001
Hospital Stay (d)	7.92±1.81	5.44±1.32	8.631	<0.001

Table 4 Comparison of Blood Indicator Levels

Blood Indicators	Control (n=57)	Treatment (n=63)	t	P
CRP (mg/L)	21.52±10.76	16.37±9.52	2.781	0.006
WBC ($\times 10^9$/L)	11.59±3.28	9.73±2.76	3.371	0.001
PLT ($\times 10^9$/L)	226.39±47.12	201.37±42.16	3.070	0.002
D-D (mg/L)	0.77±0.19	0.51±0.13	8.818	<0.001

Table 5 Comparison of Adverse Reaction Incidence

Adverse Reactions	Control (n=57)	Case (n=63)	χ^2	P
Dizziness/Headache	1	2	–	–
Nausea/Vomiting	2	2	–	–
Gastrointestinal	2	3	–	–
Skin Reaction	1	2	–	–
Hypoglycemia	1	0	–	–
Total Incidence (%)	12.28%	14.29%	0.104	0.747

Comparison of Adverse Reaction Incidence

The adverse reaction incidence in the control group was 12.28%, while in the case group, it was 14.29%. The comparison between the adverse reaction incidences in the two groups showed no significant difference ($P > 0.05$). Refer to Table 5 for details.

Discussion

Mycoplasma pneumoniae is a common ailment in children, closely associated with Mycoplasma respiratory infections.[7] Analyzing the pathogenesis of *Mycoplasma pneumoniae*, respiratory secretions tested from 2–3 days before the onset of pneumonia in children infected with Mycoplasma, up to several weeks post-recovery, consistently show the presence of Mycoplasma. Furthermore, the pathogen resides in the middle of ciliated epithelium post-infection, without invading the lung parenchyma. The cell membrane of *Mycoplasma pneumoniae* harbors numerous neurotransmitter receptors, promoting adhesion to human respiratory epithelial cells. This disrupts the normal movement of respiratory cilia, causing damage to epithelial cells and generating hydrogen peroxide, leading to localized tissue injury.[8] Combining clinical practice and analysis, children, after Mycoplasma infection, exhibit heightened sensitivity to Mycoplasma and its related metabolic products, which can trigger humoral immunity and subsequently lead to illness. However, adults possess Mycoplasma antibodies, resulting in a lower risk of disease occurrence.[9] Summarizing the impact of *Mycoplasma pneumoniae* in children post-occurrence, the following symptoms may manifest: ① High Fever: Prolonged high fever symptoms can persist in children for several weeks. ② Cough: *Mycoplasma pneumoniae* presents with paroxysmal dry cough 2–3 days after onset, which progresses to persistent cough with thickened sputum containing traces of blood. In very few cases, children might experience pain during coughing, which can last for weeks.[10] Additionally, in some cases with rapid inflammation progression, severe wheezing and breathing difficulties may occur, posing a challenge in diagnosis and treatment. Clinical analysis suggests that after children develop Mycoplasma pneumoniae, it can lead to

the following effects on their bodies: ① Compromised lung function: It can lead to symptoms of sputum production, potentially reducing the child's quality of life. ② Secondary complications: If left untreated promptly, *Mycoplasma pneumoniae* can trigger complications in the digestive and nervous systems, exacerbating persistent lung damage and even limiting the growth of toddlers.[11] Therefore, it is recommended that clinicians consider combination therapies for children with *Mycoplasma pneumoniae* to enhance treatment effectiveness.

A new class of antibiotics may serve as a crucial defense against the growing threat posed by antibiotic-resistant pathogens, specifically gram-negative bacteria. These bacteria are notoriously difficult to eliminate due to their resilient cell walls, which render many common antibiotics ineffective. Their ability to endure in harsh environments allows them to survive outside a host for extended periods, increasing the risk of subsequent infections. Compounding this issue, the effectiveness of existing antibiotics against gram-negative bacteria is diminishing, as many species have developed resistance over time.[12]

Treatment Strategies for Mycoplasma Pneumonia in Children

Mycoplasma, lacking a cell wall, falls between bacteria and viruses in the microbial spectrum and is transmitted through the air. In children, Mycoplasma rapidly circulates within the body post-infection, characterized by slow onset and high infectivity, making it a high-risk factor for pediatric pneumonia. Presently, macrolides are commonly used in clinical treatment for Mycoplasma pneumoniae, with erythromycin being the conventional choice.[13] *Oral doxycycline* has a bitter taste, exhibits resistance against various Gram-positive bacteria similar to penicillin, and has an oral absorption rate ranging between 18–45%.[14] Moreover, it poses a risk to the liver and is not advisable for continuous use. However, the rising tide of bacterial resistance, largely driven by excessive antibiotic use, has intensified the search for innovative antimicrobial strategies. One promising avenue involves the study of metal uptake through bacterial metallophores. These metallophores synthesize metal chelators that facilitate the absorption of essential metal ions, which play a critical role in bacterial growth and virulence. Understanding the mechanisms of metal ion assimilation offers potential pathways to develop new therapeutics aimed at combating infectious diseases.[15] In recent years, azithromycin has gradually been employed in the treatment of Mycoplasma pneumoniae in children, showing superior antibacterial efficacy compared to *Oral doxycycline*.[16] According to related literature,[17] oral or intravenous administration of azithromycin yields excellent antibacterial effects. Azithromycin is used in treating reproductive and pulmonary infections by inhibiting bacterial protein synthesis, ensuring highly efficient antibacterial effects in anti-infective therapy, with minimal side effects and low risks.[18] Studies by Han et al[19] demonstrated that compared to sequential treatment with *Oral doxycycline*, sequential treatment with azithromycin in children with Mycoplasma pneumoniae leads to shorter recovery times, reduced medical costs, and aligns with the principles of oral administration and antibiotic use. Hence, physicians should select treatment drugs and regimens based on the condition of children with Mycoplasma pneumoniae to facilitate their recovery. In this study, the control group of children received routine symptomatic drug treatment, while the case group received additional azithromycin treatment based on the control group's therapy. The results indicated that the total effective rate of treatment was 84.21% in the control group and 96.83% in the case group, significantly higher in the latter ($P<0.05$). After treatment, the case group exhibited significantly shorter durations in fever resolution, cough disappearance, rale disappearance, chest shadow disappearance, and hospital stay compared to the control group ($P<0.05$). These findings, consistent with previous related studies,[20,21] suggest that the application of azithromycin can further enhance the effectiveness of treatment, facilitating the remission of symptoms in affected children. This could be attributed to the high blood concentration and stable efficacy of azithromycin, allowing rapid penetration into affected tissues, ensuring sustained and efficient action. Additionally, the active components of azithromycin bind to sensitive microbial 50S ribosomal subunits, disrupting microbial protein synthesis, thereby achieving a more potent antibacterial effect.

Mycoplasma pneumonia can trigger respiratory inflammation, and the levels of inflammatory factors in children will further increase with the aggravation of lung infection. Inflammatory factors like CRP, WBC play a role in the occurrence and development of Mycoplasma pneumonia. These levels can guide the assessment of a child's condition and treatment effectiveness.[22,23] The results of this study indicate that after treatment, the levels of CRP and WBC in the case group were significantly lower than those in the control group ($P<0.05$). This suggests that the use of azithromycin effectively reduces the inflammatory response in children with Mycoplasma pneumonia. The analysis suggests that this could be due

to azithromycin's ability to improve the child's immune function to some extent and exert anti-inflammatory effects. Other studies[24] have suggested that during the course of Mycoplasma pneumonia, inflammatory factors like CRP not only affect immune regulation but also damage blood vessel walls, leading to local vasculitis, resulting in a hypercoagulable state in the blood, increasing the risk of vascular occlusion and thrombosis. Another study[25] found that children with different types of Mycoplasma pneumonia showed elevated levels of PLT and D-D, indicating that a hypercoagulable state in the blood may be involved in the occurrence and development of Mycoplasma pneumonia. The results of this study demonstrate that after treatment, the levels of PLT and D-D in the case group were significantly lower than those in the control group ($P<0.05$). This suggests that the use of azithromycin effectively improves the hypercoagulable state in the blood of children with Mycoplasma pneumonia. Furthermore, in terms of safety, the results of this study indicate that the incidence of adverse reactions in the control group was 12.28%, while it was 14.29% in the case group, with no significant difference in the occurrence rate of adverse reactions between the two groups ($P>0.05$). This suggests that the addition of azithromycin does not further increase the risk of adverse reactions in children, indicating a relatively higher safety profile in medication.

It is crucial to recognize that the risk of antibiotic resistance is multifaceted. The collateral effects of antibiotics at sub-inhibitory concentrations, alongside trace metal elements, indicate that antibiotic resistance cannot be attributed solely to antibiotic therapy. Instead, it is a complex problem influenced by co-selection and the stimulation of horizontal gene transfer among bacteria. This perspective emphasizes the need for comprehensive strategies that address the various factors contributing to antibiotic resistance, highlighting the importance of careful antibiotic stewardship in clinical practice.[26]

Conclusion

Supplementing azithromycin on the basis of conventional symptomatic treatment significantly enhances the effectiveness of Mycoplasma pneumoniae pneumonia in children. It reduces the inflammatory response and improves the children's circulatory status, further facilitating their recovery. Additionally, the additional use of azithromycin did not further increase the risk of adverse reactions in children, indicating its relatively high safety profile, thus warranting clinical promotion. It's worth noting that despite achieving some positive results in analyzing the clinical efficacy of azithromycin in the treatment of pediatric Mycoplasma pneumoniae pneumonia and its impact on platelet count and D-dimer levels, this study has certain limitations: ① Sample size and source restrictions: The relatively small sample size and data from a single medical institution in this study may limit the generalizability and applicability of the results. ② Study design: Employing a retrospective analysis method, while providing valuable observational data, might not exclude potential intervention biases or other confounding factors. Randomized controlled trials could provide clearer insights into azithromycin's treatment effects. ③ Unconsidered factors: Factors such as individual differences among children, complications, or other diseases might impact the results but were not accounted for in this study. ④ Adverse event monitoring: While adverse reaction monitoring was part of this study, the differences between the observation and control groups were not significant. However, more sensitive and comprehensive methods might be necessary to monitor potential adverse events for a more comprehensive safety assessment of the drug. In summary, despite presenting some beneficial results, this study has room for improvement. In future research, adopting more rigorous study designs, enlarging sample sizes, considering additional intervention factors, among others, will help further validate and refine the role and safety of azithromycin in the treatment of pediatric Mycoplasma pneumoniae pneumonia.

Disclosure

The authors report no conflicts of interest in this work.

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