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ARTICLE

Efficacy of Pulmicort Respules Combined with Azithromycin in the Treatment of Children with Recurrent Respiratory Tract Infection Caused by Mycoplasmal Pneumonia

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Abstract

Aims/Background The drug treatment of recurrent respiratory tract infection caused by mycoplasma pneumonia (MP) has a complex background, involving the characteristics of pathogens, drug resistance, and multiple treatment methods. This study aimed to analyze the therapeutic effect of pulmicort respules and azithromycin on children with recurrent respiratory tract infection caused by MP.

Methods The clinical data of 106 children with recurrent respiratory tract infection caused by MP diagnosed in Huoqiu First People's Hospital from July 2021 to July 2023 were retrospectively analyzed. Based on different therapeutic methods, 56 children treated with azithromycin were included in the reference group, and 50 children treated with pulmicort respules and azithromycin were included in the observation group. The disappearance time of clinical symptoms, levels of inflammatory factors, immunoglobulin levels, and complications in both groups were observed and compared.

Results After treatment, the disappearance time of fever, cough, pulmonary rales, and expectoration was shorter in the observation group, compared with the reference group ($p < 0.001$). No significant difference was observed in levels of tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), or interleukin-6 (IL-6) between the two groups on the first day of admission ($p > 0.05$). After 1 week of treatment, the observation group had significantly higher levels of TNF-α, IL-2, and IL-6 compared with the reference group ($p < 0.05$). No significant difference was observed in levels of immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) between the two groups on the first day of admission ($p > 0.05$). After 1 week of treatment, the observation group had significantly lower levels of IgG, IgA, and IgM than the reference group ($p < 0.01$). This study revealed that the incidence of complications in the observation group was 16.00%, which was significantly lower than the 37.50% in the reference group ($p < 0.05$).

Conclusion In the short-term clinical treatment, the combination application of pulmicort respules and azithromycin can effectively improve the immune function of children with recurrent respiratory tract infection caused by MP and relieve their clinical symptoms.

Key words: pulmicort respules; azithromycin; mycoplasmal pneumonia; recurrent respiratory tract infection; children

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Introduction

Mycoplasmal pneumonia (MP) is a common cause of respiratory tract infection (Zão et al, 2018). After MP infection, the immune function of children may be affected, thus increasing the risk of recurrent respiratory tract infection. Recurrent

respiratory tract infection induced by MP affects the quality of life of children, and may aggravate their immune dysfunction and increase the risk of other severe complications. Infections with the respiratory pathogen MP are often chronic, recurrent, and resistant, and can persist after antibiotic treatment (Feng et al, 2020). Macrolide antibiotics are the best choice for treatment. In recent years, the resistance of this pathogen to macrolide antibiotics has increased markedly, which makes the clinical treatment of this disease more complicated (Pei et al, 2021). At the same time, the long-term treatment with macrolides may increase the incidence of nausea, vomiting, abdominal pain, diarrhea, vascular phlebitis, and liver and kidney dysfunctions (Wang et al, 2021). This may lead to long-term health problems and increased medical costs.

The main effective component of pulmicort respules is budesonide. Budesonide is a non-halogenated corticosteroid with a wide range of anti-inflammatory effects (Keshavarzi et al, 2024); it can reduce vascular permeability, inhibit the secretion of mucus, and relieve edema and spasm (Zhao et al, 2024). Budesonide is an effective drug for the treatment of bronchial asthma. This medicine can also enhance the stability of endothelial cells, smooth muscle cells, and lysosomal membranes, reduce the contraction of smooth muscle, and quickly relieve the clinical symptoms of pneumonia such as cough, shortness of breath, wheezing, and dyspnea in children. One study (Chen et al, 2023) has confirmed that pulmicort respules combined with macrolide antibiotics can relieve children's clinical symptoms and improve their immune status. When these two drugs are used in combination, azithromycin directly inhibits bacterial protein synthesis, while budesonide acts to inhibit inflammatory cell function and reduces the production of inflammatory mediators. Therefore, the two drugs can exert a synergistic effect, which is beneficial for improving efficacy and safety (Zhang et al, 2023). These effects are critical, considering the recurrent respiratory infections in children with MP, and the differences in drug resistance compared to general MP patients. However, there is relatively little clinical research on the treatment of recurrent respiratory tract infections in children with MP, and the effectiveness of the combination of the two drugs is not yet clear. Therefore, we conducted this retrospective study to analyze the effect of the two drugs on the immune function of children with recurrent respiratory tract infection caused by MP, in order to provide a reference for clinical treatment.

Methods

General Data

The clinical data of 110 children with recurrent respiratory tract infection caused by MP in Huoqiu First People's Hospital from July 2021 to July 2023 were analyzed. This was a retrospective study and therefore subjects were not randomized into groups. Instead, groups were assigned based on different treatment methods. 58 children treated with azithromycin were initially included in the reference group; one case with abnormalities of the hematopoietic system and one case with liver dysfunction were excluded, and 56 cases were finally included. 52 children treated

with pulmicort respules and azithromycin were classified as the observation group; one case with pulmonary tuberculosis and one case with bronchial asthma were excluded, and 50 cases were finally included. The guardians of children signed the informed consent voluntarily. This study adhered to the principles of the Declaration of Helsinki (2013) (World Medical Association, 2013). To minimize potential confounding factors, we collected general patient information and developed detailed inclusion and exclusion criteria.

Inclusion criteria were: (1) Children diagnosed with recurrent respiratory tract infection caused by MP (Pediatric Committee of Paediatricians Branch of Chinese Medical Doctor Association, 2017). (2) The test results of serum MP-IgM were positive. (3) Children's age was ≤14 years old.

Exclusion criteria were: (1) Children with severe visceral or hematopoietic system diseases. (2) Children with allergies to antibiotics. (3) Children with other pulmonary diseases, such as tuberculosis and bronchial asthma. (4) Children with liver or kidney dysfunction. (5) Children with congenital immune dysfunction.

Treatment Methods

Children in the reference group received routine management (maintaining smooth breathing and oxygen intake) and azithromycin (specification: 0.5 g; manufacturer: Northeast Pharmaceutical Group Shenyang NO.1 Pharmaceutical Co., Ltd.; NMPA approval No.: H20243582; origin: Shenyang, China) after admission. Azithromycin was added to 250 mL of 0.9% sodium chloride injection to reach the final concentration of 1.0~2.0 mg/mL. The children were treated with intravenous infusion, and the infusion time was not less than 60 minutes. The dosage of azithromycin was 5–10 mg/kg each time, once a day. After 3 days of medication, the drug was discontinued for 4 days, with 1 week as a course of treatment. After that, children switched to oral administration of azithromycin, and the time of switching to oral treatment was determined by clinicians according to children's clinical response.

The observation group received the aerosol therapy of azithromycin and pulmicort respules (specification: 2 mL: 1 mg; manufacturer: AstraZeneca Pty Ltd.; NMPA approval No.: HJ20140475; origin: Wuxi, China). The children were treated with atomization inhalation twice a day for 1 week and their condition was observed.

Data Collection

We collected and organized general information (age, gender, weight, admission indicators, etc.), clinical symptom data (fever, cough, pulmonary rales, sputum disappearance time), inflammatory factor levels, immunoglobulin levels, and records of complications for the two groups of pediatric patients from our hospital's electronic medical record database.

The specific detection methods for inflammatory factors are as follows: on the first day of admission and one week after treatment, enzyme-linked immunosorbent assay was used to detect tumor necrosis factor-α (TNF-α; reference range: 0.741–1.54 ng/mL), interleukin-2 (IL-2; reference range: 3.91–250 pg/mL) and

interleukin-6 (IL-6; reference range: 0.373–0.463 pg/mL). Test kits and instruments were as follows: the test kits of TNF-α, IL-2, and IL-6 were provided by Wuhan Merck Biotechnology Co., Ltd. The test kits included TNF-α kits (batch No.: T85461-CH5223; origin: Wuhan, China), IL-2 kits (batch No.: IL202101541713; origin: Wuhan, China), and IL-6 kits (batch No.: IL2020084847; origin: Hubei, China). An automatic biochemical analyzer (model: BS-600M; Guangdong Medical Products Administration Certified No.: 20152221145; manufacturer: Shenzhen Mindray Biomedical Electronics Co., Ltd.; origin: Shenzhen, China) was used in this study.

The specific detection method for immunoglobulin was as follows: immunoglobulin G (IgG; reference range: 6.0–16.0 g/L) and immunoglobulin A (IgA) levels were measured on the first day of admission and one week after treatment in the patient; reference range: 0.76–3.9 g/L) and immunoglobulin M (IgM; reference range: 0.4–3.45 g/L). An automatic protein analyzer (model: Atellica NEPH630; NMPA (I) approval No.: 20202220508; manufacturer: Siemens Healthcare Diagnostics Products GmbH; origin: Shanghai, China) was used.

The study compared the incidence of complications in the two groups. Respiratory tract infection could involve adjacent organs, including complications of sinusitis, otitis media, and peritonsillar abscess.

Incidence of complications = cases with complications/total cases $\times$ 100%.

Statistical Analysis

SPSS25.0 software (manufacturer: International Business Machines Corporation; origin: Armonk, NY, USA) was used for data processing and analysis. The Shapiro-Wilk method was to test the normality of continuous variables for comparison between groups. Non-normally distributed variables were expressed as [M (P_{25}, P_{75})], and group differences were assessed using the Mann-Whitney U test. Normally distributed variables were expressed as mean $\pm$ standard deviation and group differences were assessed using the *t*-test. Appropriate testing methods for categorical variables were based on specific situations: (1) 2 $\times$ 2 contingency tables: (i) Pearson's chi-square test when all expected frequencies T $\geq$5 and total n $\geq$ 40. (ii) If the expected frequency 1 $\leq$ T $<$ 5, and n $\geq$ 40, the chi-square with continuity correction was used. (iii) If there were expected frequencies T $<$1 or n $<$ 40, the Fisher's exact test was used. (2) R$\times$C contingency tables: If $<$20% of cells had expected frequencies less than 5, or all expected frequencies T $\geq$1, the Pearson's chi-square test was used; if $>$20% of cells had expected frequencies less than 5, or there were cells with expected frequencies T $<$1, the Fisher's exact test was used. Categorical variables were expressed as n (%). p values $<$ 0.05 were considered statistically significant.

Results

General Data

Table 1 shows that there were no significant differences in weight, age, sex, or other general data between the two groups ($p > 0.05$).

Table 1. Comparison of general data.

Projects	Observation group (n = 50)	Reference group (n = 56)	z/χ^2	p
Sex			0.189	0.664
Male	28 (56.00)	29 (51.79)		
Female	22 (44.00)	27 (48.21)		
Age [years old, M (P_{25}, P_{75})]	6.50 (5.00, 8.00)	6.30 (4.00, 9.00)	–0.191	0.848
Height [cm, M (P_{25}, P_{75})]	121.15 (96.30, 136.90)	116.40 (94.20, 144.35)	–0.146	0.884
Weight [kg, M (P_{25}, P_{75})]	29.05 (18.60, 41.20)	31.25 (22.00, 42.60)	–0.316	0.752
Temperature at admission [°C, M (P_{25}, P_{75})]	39.65 (38.40, 40.00)	39.60 (38.80, 40.40)	–0.899	0.368
Imaging manifestations			0.504	0.777
Parenchymal infiltration of pulmonary lobule	37 (74.00)	38 (67.86)		
Idiopathic pulmonary infiltration	9 (18.00)	12 (21.43)		
Consolidation of pulmonary segment/lobe	4 (8.00)	6 (10.71)		
Pulmonary complications			0.009	0.924
Atelectasis	7 (14.00)	7 (12.50)		
Pleural effusion	5 (10.00)	6 (10.71)		

Table 2. Comparison of clinical symptoms between groups [d, M (P_{25}, P_{75})].

Symptoms	Observation group (n = 50)	Reference group (n = 56)	z	p
Fever	6.00 (5.00, 7.00)	8.00 (6.50, 10.00)	–5.030	<0.001
Cough	5.00 (4.00, 6.00)	8.00 (7.00, 10.00)	–6.746	<0.001
Pulmonary rales	5.00 (4.00, 7.00)	8.00 (7.00, 10.00)	–5.892	<0.001
Expectoration	3.50 (2.00, 4.00)	5.00 (4.00, 6.00)	–4.778	<0.001

Clinical Symptoms

Table 2 shows that the disappearance time of cough, pulmonary rales, fever, and expectoration in the observation group was shorter compared with the reference group ($p < 0.001$). This indicates that the treatment plan of the observation group can alleviate the symptoms of recurrent respiratory tract infections in children with MP in a shorter period of time.

Inflammatory Factors

No significant differences were observed in levels of TNF-α, IL-2, and IL-6 between the two groups on the first day of admission ($p > 0.05$). After 1 week of treatment, the observation group had significantly lower levels of TNF-α, IL-2, and IL-6 than the reference group ($p < 0.01$), as shown in Table 3. This indicates that the treatment plan of the observation group has a significant therapeutic effect on inflammation control in children with recurrent respiratory tract infections.

Immunoglobulin

No significant differences were observed in levels of IgG, IgA, and IgM between the two groups on the first day of admission ($p > 0.05$). After 1 week of

Table 3. Comparison of inflammatory factors between the two groups [M (P_{25}, P_{75})].

Indicators	Time	Observation group (n = 50)	Reference group (n = 56)	z	*p*
TNF-α (ng/mL)	First day of admission	18.65 (15.40, 21.40)	17.30 (13.30, 19.85)	–1.437	0.151
	After 1 week of treatment	2.45 (1.80, 3.60)	6.35 (4.35, 9.05)	–7.713	<0.001
IL-2 (pg/mL)	First day of admission	430.95 (382.40, 485.60)	444.60 (380.85, 484.05)	–0.313	0.754
	After 1 week of treatment	188.05 (142.50, 230.80)	250.80 (225.90, 292.05)	–5.930	<0.001
IL-6 (pg/mL)	First day of admission	0.94 (0.72, 1.15)	1.01 (0.81, 1.18)	–0.798	0.425
	After 1 week of treatment	0.60 (0.46, 0.65)	0.88 (0.74, 0.96)	–7.578	<0.001

TNF-α, tumor necrosis factor-α; IL-2, interleukin-2; IL-6, interleukin-6.

Table 4. Comparison of immunoglobulin levels between groups [g/L, M (P_{25}, P_{75})].

Indexes	Time	Observation group (n = 50)	Reference group (n = 56)	z	*p*
IgG	First day of admission	4.10 (2.70, 6.10)	4.80 (2.80, 6.75)	–0.937	0.349
	After 1 week of treatment	13.65 (11.90, 15.40)	8.80 (7.30, 10.90)	–7.355	<0.001
IgA	First day of admission	0.52 (0.36, 0.75)	0.58 (0.34, 0.84)	–0.680	0.496
	After 1 week of treatment	2.84 (1.99, 3.54)	1.93 (1.28, 2.50)	–3.731	<0.001
IgM	First day of admission	0.58 (0.32, 0.74)	0.45 (0.26, 0.65)	–1.896	0.058
	After 1 week of treatment	2.31 (1.63, 3.05)	1.82 (1.25, 2.33)	–2.801	0.005

IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.

treatment, the observation group had significantly higher levels of IgG, IgA, and IgM than the reference group ($p < 0.05$), as shown in Table 4. This indicates that the treatment plan of the observation group can effectively improve the immunoglobulin levels in children with recurrent respiratory tract infections caused by MP.

Incidence of Complications

Table 5 shows that the incidence of complications in the observation group was 16.00%, which was significantly lower than the 37.50% in the reference group ($p < 0.05$). This indicates that the treatment plan of the observation group has better safety.

Discussion

MP is one of the main causes of upper and lower respiratory tract infection in school-age children (Biagi et al, 2021). MP infection can cause direct pulmonary injury and immune injury (Zhang et al, 2022). Recurrent respiratory tract infection caused by MP leads to shortness of breath, wheezing, and dyspnea, and severe infections can lead to asphyxia, which must be handled carefully. Azithromycin is a synthetic macrolide antibiotic that can effectively fight against various bacterial and mycobacterial infections (Oliver and Hinks, 2020), and is highly effective in the treatment of MP. However, the cardiovascular and gastrointestinal adverse effects of azithromycin have been known since its clinical administration for

Table 5. Comparison of incidence of complications between the two groups [n (%)].

Indicators	Observation group (n = 50)	Reference group (n = 56)	χ^2	p
Nasal sinusitis	4 (8.00)	9 (16.07)	-	-
Otitis media	3 (6.00)	7 (12.50)	-	-
Peritonsillar abscess	1 (2.00)	5 (8.93)	-	-
Incidence of complications	8 (16.00)	21 (37.50)	6.144	0.013

bacterial pneumonia nearly half a century ago. Moreover, antibiotic resistance is an increasingly serious limitation of this therapy (Firth and Prathapan, 2020). Budesonide is a glucocorticoid, which is characterized by its local effect and low systemic bioavailability (Olivas et al, 2021). The physicochemical and pharmacokinetic/pharmacodynamic properties of inhaled budesonide enable it to achieve rapid and high airway efficacy (Tashkin et al, 2019). Budesonide combined with azithromycin has significant clinical benefits in the treatment of recurrent respiratory tract infection caused by MP.

The results of this study showed that the duration of clinical symptoms of cough, pulmonary rales, fever, and expectoration was shorter in the observation group compared with the reference group, indicating greater efficacy of the combined drug therapy for the treatment of clinical symptoms. Pulmicort respules can effectively inhibit the development of inflammation, alleviate smooth muscle spasm, and stimulate endothelial function (Chu et al, 2023), thereby relieving clinical symptoms. This is similar to the conclusion of Xu et al (2024) that aerosol inhalation therapy of high-dose budesonide can improve the lung function and alleviate clinical symptoms of patients. The results of the present study also showed that after 1 week of treatment, the levels of TNF-α, IL-2, and IL-6 in the observation group were significantly lower compared with the reference group. These results indicate that combined drug therapy can effectively reduce the inflammatory response in children with recurrent respiratory tract infection caused by MP. The mechanism relates to the partial interaction between glucocorticoid receptors and pyruvate dehydrogenase complexes. Glucocorticoids increase the activity of the complexes and cause accelerated flux of the tricarboxylic acid cycle in pro-inflammatory macrophages. This glucocorticoid-mediated rewiring of mitochondrial metabolism enhances the tricarboxylic acid cycle-dependent production of itaconic acid throughout the inflammatory response, which interferes with the production of pro-inflammatory cytokines (Auger et al, 2024).

Glucocorticoids have strong anti-inflammatory, immunosuppressive effects, and pleiotropic effects on innate and adaptive immune responses (Ikuta et al, 2022). The results of this study showed that after 1 week of treatment, the observation group had significantly higher levels of IgG, IgA, and IgM than the reference group, indicating that combined therapy can effectively improve children's immune status. These effects are critical because children with recurrent respiratory tract infection often have insufficient immune response. Glucocorticoids inhibit antigen-stimulated inflammation mediated by macrophages, dendritic cells, and epithelial cells, inhibit the cytotoxic immune response through down-regulating the produc-

tion of interferon γ and inhibiting the development of type 1 helper T cells, $CD^{8+}T$ cells, and natural killer cells, and activate other aspects of the immune system (Shimba and Ikuta, 2020). These effects are beneficial to children's immune function.

By comparing the incidence of complications in the two groups, this study found that the incidence of complications was 16.00% in the observation group, which was significantly lower than the 37.50% in the reference group, indicating that combined drug treatment can reduce the rate of adverse complications in children with MP. Combined drug treatment administered through aerosol inhalation can significantly reduce mucosal injury and inflammatory reaction in the throat, nasopharynx, and other areas, thus reducing the complications of respiratory tract infection in children with MP.

There are some limitations in this study. This was a single-center study with a small sample size, which may lead to a lack of universality, low accuracy of research results, and limited applicability. As a retrospective study based on pre-existing clinical data, there may have been bias in patient selection. In this study, it was not possible to completely control for the influence of all potential confounding factors, which may lead to inaccuracy in the results.

We offer several suggestions for future research. Firstly, to control for potential confounding factors and to improve the accuracy and universality of research results, a multicenter prospective study should be conducted. Secondly, further research is needed to determine the clinical efficacy of combining two drugs at different doses. In addition, in-depth research should be conducted on the exact therapeutic effects on children in different age ranges to provide higher-quality evidence for clinical practice.

Conclusion

In summary, the combination application of pulmicort respules and azithromycin in children with recurrent respiratory tract infection caused by MP has achieved good results in short-term clinical practice. This method is conducive to improving the immune function of children, reducing clinical symptoms and inflammatory responses, and reducing the complication rate of respiratory tract infection involving adjacent organs.

Key Points

- Pulmicort respules combined with azithromycin can alleviate the clinical symptoms of children with recurrent respiratory tract infection caused by mycoplasmal pneumonia (MP).
- Pulmicort respules combined with azithromycin can reduce the inflammatory response in children with recurrent respiratory tract infection caused by MP.
- Pulmicort respules combined with azithromycin is effective for improving the immune function of children with recurrent respiratory tract infection caused by MP.
- Pulmicort respules combined with azithromycin can reduce the incidence of complications of recurrent respiratory tract infection caused by MP.

Availability of Data and Materials

The datasets used and/or analyzed during the current study were available from the corresponding author on reasonable request.

Author Contributions

JK designed the study; all authors conducted the study; XQT collected and analyzed the data. JK and XQT participated in drafting the manuscript, and both authors contributed to critical revision of the manuscript for important intellectual content. Both authors gave final approval of the version to be published. Both authors participated fully in the work, take public responsibility for appropriate portions of the content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study adhered to the principles of the Declaration of Helsinki (2013). This study has been approved by the Medical Ethics Committee of Huoqiu First People's Hospital (Approval No.: 20230015). The guardians of children signed the informed consent voluntarily.

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Conflict of Interest

The authors declare no conflict of interest.

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