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Effects of a combination of erythromycin sequential therapy and azithromycin on lung function and inflammatory factors in children with severe mycoplasma pneumonia

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Abstract: This study aimed to investigate the effect of erythromycin sequential therapy plus azithromycin on lung function and inflammatory factors in children with severe mycoplasma pneumonia (MP). Ninety-three severe MP children were selected and randomized into azithromycin group, erythromycin group, and combination group, 31 cases in each. The disappearance time of cough, fever, lung rale and X-ray shadow in the combination group were shorter than those in the azithromycin group and erythromycin group. The clinical treatment efficiency of the combination group was higher than that of the azithromycin group. After treatment, FVC, FEV1/FVC and PEF in combination group were higher than before treatment; IL-8, IL-6, CRP in combination group were lower than erythromycin group and azithromycin group. IL-8, IL-6, CRP are negatively correlated with disappearance time of cough, fever, pulmonary rale, X-ray shadow and clinical treatment efficiency; FEV1/FVC is positively correlated with disappearance time of cough and fever, pulmonary rales and X-ray shadow, and clinical treatment efficiency. Sequential erythromycin therapy combined with azithromycin in the treatment of MP can effectively inhibit high inflammatory reactions, control the disease in a timely manner, improve lung function and produce fewer adverse reactions.

Keywords: Erythromycin sequential therapy, azithromycin, severe mycoplasma pneumonia, lung function, inflammatory factors.

INTRODUCTION

Mycoplasma pneumonia in children, characterized by diversified epidemiological characteristics, complex pathophysiology and rapid disease progression, can result in life-threatening condition such as atelectasis, lung consolidation and even damage to multiple organs of the heart, brain, and liver once evolves into severe mycoplasma pneumonia (Krafft and Christy, 2020; Lee *et al.*, 2018). The pneumonia diseases and related symptoms are stemmed from the adhesion of mycoplasma pneumoniae and host cells, and it is widely believed that repeated infections of inflammatory factors and lung infections caused by strong stress responses are the underlying pathological mechanism of severe mycoplasma pneumoniae in children (Søndergaard *et al.*, 2018; Waites *et al.*, 2017). Macrolides, including azithromycin and erythromycin, harbor excellent effects on controlling over inflammation, and are frequently used in the treatment of mycoplasma pneumonia with a definitive effectiveness (Wang and Yang, 2018). Discouragingly, large shadows of the lungs can be detected from X-ray examination when seeking medical treatment due to the hidden clinical symptoms of children with severe pneumonia following the onset of the disease, as a result, the inhibition of strong inflammation and the improvement of lung function by conventional antibiotics are not significant (Dai *et al.*, 2021). It is generally agreed that infection suppression is considered that the inflammatory factors are reduced to normal levels. Previously published literature has found that interleukin-6 (IL-6) in children treated with azithromycin for two weeks obtain a substantial decrease, but not for IL-8 and C-reactive protein (CRP) (Chen *et al.*, 2016). Additionally, apparent side effects of children with single use of antibiotics are also observed. Currently, sequential therapy has been clinically introduced to control the disease while ensuring safe drug concentration. When erythromycin and azithromycin are used in combination, both two drugs have immunosuppressive and anti-inflammatory effects, which can compensate for the limitations of single medication (Schuster Bruce *et al.*, 2017). At present, erythromycin sequential therapy has been used in mycoplasma pneumonia, yet there are still several urgent problems to be addressed, such as dosage, the half maximal inhibitory concentration (IC_{50}) of drug-containing plasma, drug action mechanism, etc. (Li *et al.*, 2021). Therefore, this study applied erythromycin sequential therapy combined with azithromycin in the treatment of children with mycoplasma pneumonia,

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explored its influence on inflammatory factors and lung function, and clarified its mechanism of action and its correlation with clinical characteristics, aiming to provide references for the choice of drugs.

MATERIALS AND METHODS

General information

Ninety-three children with mycoplasma pneumonia admitted and diagnosed in our hospital from February 2020 to February 2021 were recruited. All patients were randomly assigned into azithromycin group, erythromycin group and combination group, 31 cases each. There were 18 males and 13 females in the azithromycin group, with an average of (7.48±2.10) years old and an average course of (2.44±0.62) days; 20 males and 11 females in the erythromycin group, with an average of (7.30±2.07) years old and an average course of disease (2.50±0.59) days; in the combination group, there were 19 males and 12 females, with an average age of (7.44±2.11) years and an average duration of (2.48±0.51) days. The baseline data of the three groups were similar (P>0.05). The study was approved by the Medical Ethics Society, and the children's family members signed written informed consent.

Inclusion criteria

(1) Diagnosed as mycoplasma pneumonia by a specialist physician with more than five years' experience based on clinical manifestations, laboratory and chest X-ray examinations, and conformed to the Expert Consensus on the Diagnosis and Treatment of Mycoplasma Pneumoniae Pneumonia in Children (Houdouin *et al.,* 2014).
(2) Aged 3~14 years old;
(3) No previous treatment for mycoplasma pneumoniae infection within half a year, and no repeated admission within 3 months;
(4) Tolerant and not allergic to the treatment in this study;
(5) No extra pulmonary complications.

Exclusion criteria

(1) Congenital heart disease;
(2) Other system diseases including but not limited to viral hepatitis, tuberculosis, mycoplasma infection, respiratory failure, etc.;
(3) Two or more organs and system function damage;
(4) Use of immunization regulators or hormone drugs within 3 months;
(5) Other infections or bleeding.

Treatment Method

Azithromycin group Azithromycin (Pfizer Pharmaceutical Co., Ltd., SFDA approval number: J20140073, specification: 0.5 g/bottle) was dissolved in 0.9% sodium chloride solution for intravenous infusion and the infusion concentration was 1~2mg/mL, 1 time/ d at a dose of 10 mg/kg, and the treatment was for 14 days.

Erythromycin group: Erythromycin lactobionate (Chengdu No. 1 Pharmaceutical Co., Ltd., SFDA approval number: H51023236, specification: 0.5g/bottle) was dissolved in 10ml of sterile water for injection and 1ml sodium bicarbonate was added to every 100 ml solution to ensure that the concentration of erythromycin maintaining 1%~5%; then it was injected slowly intravenously at a dose of 25mg/kg (divided into two infusions) on days 1 to 3, and at a dose of 5mg/kg on days 4 to 14.

Combination group: Erythromycin lactobionate was instilled at a dose of 25 mg/kg/d for 3 days, followed by azithromycin dry suspension (Pfizer Pharmaceutical Co., Ltd., SFDA approval number: H10960112, specification: 0.1 g*6 Bag) orally, and the total treatment cycle is 14 days.

Outcome measures

(1) Symptoms and X-ray shadow disappearance time. The disappearance of cough, fever, lung wet rales, and X-ray shadow were recorded;

(2) Clinical efficacy. It was evaluated based on clinical symptoms and chest X-ray examination; the treatment effectiveness was considered significant effective if cough, fever, pharynx pain and other clinical symptoms and signs were significantly reduced, lung auscultation was normal, lung shadows were basically absorbed. The treatment was deemed effective if cough, fever, sore throat, etc. were reduced, a small number of wet rales were heard in the lungs and a small amount of lung shadows were absorbed. The treatment was considered ineffective if cough, fever, sore throat and other clinical symptoms and signs and lung shadows had no significant changes or aggravation. Treatment effectiveness (%) = (significantly effective + effective) / total number of cases × 100%.

(3) Pulmonary function indicators. Master Screen PFT pulmonary function meter (German JAEGE company) was used to detect lung function indicators such as forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF) and operated by a respiratory specialist with more than five years of clinical experience; the instrument should be debugged and calibrated before use, and the research participants were tested three times in a quiet state and the optimal value was obtained; if the optimal value of FEV1/FVC was less than 70%, bronchodilation experiments should be performed three times to obtain the optimal value.

(4) Inflammatory factors. 3mL of venous blood was drawn before and after treatment, placed in a vacuum blood collection tube containing coagulant, centrifuged at 4°C, 3000r/mL for 15 minutes within 20 minutes; then the serum was isolated and placed at -80°C in the refrigerator; Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of IL-8, IL-6 and CRP. All operation

were strictly performed in accordance with the instructions.

(5) Plasma concentration. Venous blood within half an hour after the end of the third day of medication was drawn and the concentration was detected by HPLC with reference to the instructions of 7rDx erythromycin blood concentration detection reagent (Pfizer Pharmaceutical Co., Ltd.) and azithromycin blood concentration detection reagent (Pfizer Pharmaceutical Co., Ltd.); the plasma concentration of erythromycin was measured again at 14 days after the drug administration and at the time of discharge; the plasma concentration of the drug was used as the independent variable, and the treatment rate was used as the dependent variable to map a concentration-effect curve and analyze the therapeutic effect of different concentrations of medicated plasma on diseases; the regression analysis was performed with treatment rate as dependent variable to calculate the IC_{50} of each drug-containing plasma.

(6) Adverse reaction rate. The number of cases of vomiting, diarrhea, skin rash, phlebitis, confusion, arrhythmia, etc. was recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS19.0 software. The measurement data among multiple groups were compared by ANOVA one-way analysis of variance, pairwise comparison was performed by Snk-q test, and the paired sample t test was used before and after treatment within the group; the count data were compared by chi-square non-correction method (χ^2) or *Fisher's* exact test; *Spearman* correlation coefficient analysis was performed to analyze the relationship between lung function, inflammatory factors and clinical symptoms of mycoplasma pneumonia. Statistical difference was assumed at $P<0.05$.

RESULTS

Symptoms and X-ray shadows disappearance time

The disappearance time of cough, fever, lung rale and X-ray shadow in the combination group were shorter than those in the azithromycin group and erythromycin group, and those in the erythromycin group were shorter than the azithromycin group ($P<0.05$), as presented in table 1.

X-ray film examination

Fig. 1 is a chest radiograph of an 11-year-old female child with mycoplasma pneumonia before and after treatment: before treatment, right lower lung parenchymal infiltrating lesions (large consolidated shadows), and part of the lung insufficiency was identified (fig. 1A); After treatment, right lower lung parenchymal infiltrating lesion was basically absorbed (fig. 1B).

Clinical treatment efficiency

The clinical treatment efficiency of the combination group was higher than that of the azithromycin group ($P<0.05$), and there was no significant difference in clinical treatment efficiency among the other groups ($P>0.05$), see table 2.

Lung function indicators

There was no significant difference in FVC, FEV1/FVC, PEF between the three groups before treatment ($P>0.05$); after treatment, FVC, FEV1/FVC, PEF in the three groups increased, and FEV1/FVC in the azithromycin group and erythromycin group after treatment was higher than before treatment ($P<0.05$), FVC, FEV1/FVC, PEF after treatment in the combination group were all higher than before treatment ($P<0.05$); see table 3.

Serum inflammatory factors

Before treatment, there was no significant difference in IL-8, IL-6 and CRP among the three groups ($P>0.05$); after treatment, IL-8, IL-6 and CRP in each group were lower than before treatment ($P<0.05$); After treatment, IL-8, IL-6 and CRP in the combination group were lower than those in the erythromycin group and azithromycin group ($P<0.05$), and the IL-8, IL-6 and CRP in the erythromycin group were lower than those in the azithromycin group ($P<0.05$), as listed in table 4.

Correlation between inflammatory factors, lung function and the disappearance time of clinical symptoms of mycoplasma pneumonia and clinical treatment efficiency

IL-8, IL-6, CRP are negatively correlated with disappearance time of cough, fever, pulmonary rale, X-ray shadow, and clinical treatment efficiency ($P<0.05$); FEV1/FVC is negatively correlated with disappearance time of cough, fever, pulmonary rale, X-ray shadow, and clinical treatment efficiency were positively correlated ($P<0.05$); see table 5.

Plasma concentration

The results showed that the plasma concentrations of the three groups were all within the safe range, and the difference was not statistically significant ($P>0.05$), see table 6. The IC50 of the azithromycin group, the erythromycin group and the combination group were (2.03±0.25)%, (1.88±0.17)%, (1.22±0.15)%, respectively. The IC50 of the combination group was lower than that of the azithromycin group and erythromycin group ($P<0.05$), and the erythromycin group was lower than that in the azithromycin group ($P<0.05$).

Logistic regression analysis of risk factors for ineffective treatment

Taking all ineffective cases as a whole (ineffective=1, markedly effective+effective=0), the treatment plan, lung function, and inflammatory factors were used as independent variables to perform *Logistic* regression

Table 1: Comparison of disappearance time of symptoms and X-ray shadows (n=31, x±s, d)

Groups	disappearance time of cough	disappearance time of fever	disappearance time of lung wet rales	disappearance time of X-ray shadows
Azithromycin group	8.59±1.24	4.44±0.50	9.44±1.35	7.20±1.05
Erythromycin group	6.11±1.17[a]	3.25±0.41[a]	7.18±1.10[a]	5.11±0.78[a]
Combination group	5.32±1.03[ab]	2.68±0.22[ab]	5.22±0.86[ab]	3.66±0.62[ab]

Note: Compared with the azithromycin group, [a]P<0.05; compared with the erythromycin group, [b]P<0.05

Table 2: Comparison of clinical treatment efficiency of the three groups [n (%), n=31]

Groups	Significantly effective	Effective	Ineffective	Clinical efficacy
Azithromycin group	8(25.81)	12(38.71)	11(35.48)	20(64.52)
Erythromycin group	12(38.71)	13(41.94)	6(19.35)	25(80.65)
Combination group	16(51.61)	13(41.94)	2(6.45)	29(93.55)[a]

Note: Compared with the azithromycin group, [a]P<0.05

Table 3: Comparison of three groups of lung function indicators (x±s, n=31)

Groups	Time	FEV1(L)	FEV1/FVC	PEF(L/s)
Azithromycin group	Before treatment	0.73±0.20	0.62±0.11	7.22±2.03
	After treatment	0.79±0.22	0.70±0.13[a]	7.88±2.16
Erythromycin group	Before treatment	0.75±0.21	0.63±0.12	7.20±2.06
	After treatment	0.84±0.23	0.73±0.15[a]	8.10±2.21
Combination group	Before treatment	0.72±0.22	0.60±0.13	7.23±2.05
	After treatment	0.87±0.24[a]	0.77±0.15[a]	8.44±2.25[a]

Note: Compared with before treatment within the group, [a]P<0.05

Table 4: Comparison of serum inflammatory factor levels in the three groups (x±s, n=31)

Groups	Time	IL-8(pg/ml)	IL-6(pg/ml)	CRP(mg/L)
Azithromycin group	Before treatment	54.25±3.39	105.24±13.32	36.25±8.21
	After treatment	26.26±3.89[a]	49.14±7.68[a]	19.10±3.02[a]
Erythromycin group	Before treatment	55.03±6.21	105.02±11.03	36.44±5.25
	After treatment	20.58±4.21[ab]	40.36±6.56[ab]	13.23±7.34[ab]
Combination group	Before treatment	54.42±7.03	105.77±12.28	37.21±3.02
	After treatment	16.17±1.02[abc]	30.03±4.31[abc]	8.11±2.36[abc]

Note: Compared with before treatment within the group, [a]P<0.05; compared with the azithromycin group, [b]P<0.05; compared with the erythromycin group, [c]P<0.05

Table 5: Correlation between inflammatory factors, lung function, disappearance time of clinical symptoms of mycoplasma pneumonia and clinical treatment efficiency

Disappearance time of symptoms	IL-8	IL-6	CRP	FEV1	FEV1/FVC	PEF
Cough	0.201[a]	0.262	0.213	0.025[a]	-0.201	-0.015
Fever	0.210[a]	0.241	0.240	0.110[a]	-0.215	-0.101
Lung wet rales	0.354[b]	0.245	0.339	0.125[b]	-0.387	-0.118
X-ray shadow	0.320[b]	0.305	0.248	0.089[a]	-0.320	0.130
Clinical treatment efficiency	0.226[b]	0.224	0.305	0.044[a]	-0.227	0.059

Note: [a] represents a significant correlation when the confidence index (two-sided) is 0.05; [b] represents a significant correlation when the confidence index (two-sided) is 0.01

Table 6: Comparison of plasma concentration (n=31, x±s, ug/mL)

Groups	Drugs	3 d after treatment	14 dafter treatment	At discharge
Azithromycin group	Azithromycin	11.50±1.21	3.54±0.31	2.78±0.59
	Erythromycin	6.30±1.03*	2.22±0.52*	1.66±0.38*
Erythromycin group	Azithromycin	11.38±1.15	3.46±0.36	3.04±0.41
	Erythromycin	6.22±1.04*	2.18±0.44*	1.57±0.33*
Combination group	Azithromycin	11.44±1.22	3.52±0.33	2.90±0.38
	Erythromycin	6.32±1.05*	2.24±0.41*	1.60±0.40*

Note: Compared with the azithromycin group, *P<0.05

Table 7: Logistic regression analysis of risk factors for ineffective treatment

Factors	β	S.E	Wald	OR(95%CI)	*P*
Treatment scheme (take the azithromycin group as a reference)					
Erythromycin group	0.302	0.147	15.001	1.039(0.001-1.078)	0.125
Combination group	1.221	0.325	6.306	0.376(0.127-0.996)	0.001
IL-8	0.895	0.231	2.010	1.110(1.017-1.211)	0.041
IL-6	0.053	0.032	2.681	1.801(0.577-3.976)	0.054
CRP	0.854	0.320	5.435	1.025(1.001-1.050)	0.014
FEV1	0.054	0.028	3.687	0.787(0.130-2.446)	0.122
FEV1/FVC	0.574	0.217	6.341	0.720(0.528-0.943)	0.010
PEF	0.623	0.224	3.004	2.670(0.448-4.924)	0.154

Table 8: The sensitivity and specificity of lung function and inflammatory factors in predicting clinical treatment efficiency after treatment

Index	sensitivity	Specificity	Coincidence rate	Positive prediction rate	Negative prediction rate
IL-8	42.69	58.47	61.71	41.02	20.69
IL-6	43.02	57.01	66.42	38.20	18.22
CRP	53.34	74.02	57.61	35.25	22.36
FEV1	69.36	75.24	77.89	42.65	35.24
FEV1/FVC	50.32	69.65	65.30	35.25	30.05
PEF	59.69	63.02	88.89	50.20	38.69

Table 9: Comparison of adverse reaction rates among the three groups [n(%), n=31]

Groups	diarrhea	rashes	Phlebitis	Arrhythmia	Vomiting
Azithromycin group	2	0	3	1	4
Erythromycin group	1	1	2	0	2
Combination group	1	0	1	0	1

analysis. The results showed that IL-8 and CRP are the risk factors of ineffective treatment (OR>1, P<0.05), the combination group, FEV1/FVC are protective factors for ineffective treatment (OR<1, P<0.05), see table 7.

The sensitivity and specificity of lung function and inflammatory factors in predicting clinical treatment efficiency after treatment

After treatment, the sensitivity and specificity of lung function and inflammatory factors in predicting clinical treatment efficiency are all lower than 75%, as shown in table 8.

Adverse reaction rate

The three groups mainly developed diarrhea, skin rash, phlebitis, arrhythmia and vomiting, and one or more adverse reactions may concur. There was no significant difference in the adverse reaction rate between the three groups (P>0.05), see table 9.

DISCUSSION

Mycoplasma pneumonia is essentially the host's autoimmune damage caused by the release of IL-1, IL-8, interferon-γ (IFN-γ) and other cytokines (Remmelts *et al.*,

2012). Prior clinical data show that severe mycoplasma pneumonia in the pediatric ward is the main cause of multiple organ and system involvement in children. It is currently believed that the pathogenesis of mycoplasma pneumonia may include immune dysfunction, the influence of inflammatory mediators, damage to organs outside the lung, and granulation hyperplasia (Kutty *et al.*, 2019). Study in tissue biopsy found that while inflammation promotes the death of inflammatory factors in the lungs, it can also promote the proliferation and infiltration of inflammatory cells (McGarry *et al.*, 2018). Based on the pathogenesis of the disease, the macrolide drug azithromycin is not outstanding enough in effectively reducing inflammatory factors and improving immune function and it is prone to adverse reactions such as anaphylactic shock, skin rash or hearing impairment (Doan *et al.*, 2020). It is speculated to be related to the high plasma concentration in the tissues, the concentration of the inflammation site being more than six times higher than the non-inflammatory site, and the half-life of 35~48 h (Takata *et al.*, 2011).

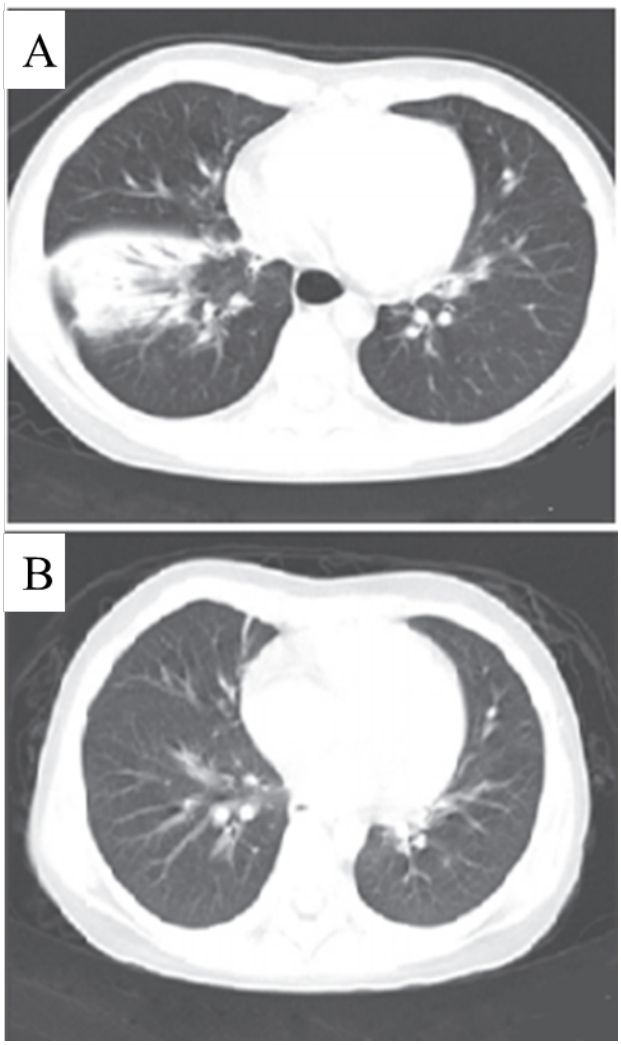

Fig. 1: Chest X-ray before (A) and after (B) treatment

Sequential therapy is a new type of therapy, wherein the disease is firstly controlled by intravenous infusion of drugs, and followed by oral drugs after the disease is stable (Read *et al.*, 2019). Erythromycin plays the strongest immunosuppressive and anti-inflammatory role, and has an extremely broad antibacterial spectrum. In addition, it presents antibacterial activity against most microorganisms such as gram-positive aerobes, gram-negative aerobes, and anaerobes. It is reported in the literature that erythromycin does not produce cross-resistance to enzyme-producing drug-resistant strains, and is tremendously effective against mixed and severe infections (Blyth and Gerber, 2018). Sequential erythromycin therapy is safe in the sense that it can quickly stabilize the condition through intravenous administration in the early stage, and the bioavailability of oral administration in the later period, the plasma concentration and the concentration of cellular drugs is high, and the gastrointestinal reaction is reduced (Liu *et al.*, 2016). The results of this study show that erythromycin sequential therapy combined with azithromycin can quickly improve the clinical symptoms and imaging manifestations of children; moreover, the inflammatory factors and lung function after treatment were improved more significantly, and the clinical efficacy was remarkably high. This is basically consistent with previous reports conducted by Chen et al. who applied erythromycin sequential therapy to treat mycoplasma pneumonia and concluded that it can reduce the permeability of the capillary wall and reduce inflammatory exudation, and is of greater value for the recovery of immune function (Chen and Zhang, 2018). The pharmacological properties of erythromycin determine that it can achieve more promising effects through sequential therapy. In this study, the analysis of erythromycin plasma concentration and IC50 found that erythromycin sequential therapy combined with azithromycin oral administration can guarantee the curative effect and the lowest and safe plasma concentration as well. The effective blood concentration of erythromycin is 2~6ug/ml and reaches the peak value at 3 days after administration. Excessive concentration can directly cause nausea and arrhythmia. Erythromycin is an exogenous hormone with weak effect and a large dose of erythromycin within a safe range can realize an excellent effect.

Further analysis of the relationship between inflammatory factors, lung function and clinical symptoms found that IL-8, IL-6, CRP, FEV1/FVC are significantly related to the disappearance time of clinical symptoms and clinical treatment efficiency, and they can be used as sensitive indicators to evaluate the efficacy. It demonstrates that changes in lung function and inflammatory factors are involved in pharmacological effects (Emami Ardestani and Zaerin, 2015). Erythromycin can significantly reduce airway hyperresponsiveness and improve the degree of

inflammation and lung function and the enhancement is achieved by adding azithromycin. CRP is an important indicator reflecting the degree of inflammation, with lower concentration in healthy people and higher in acute infection and tissue damage. Among patients with severe pneumonia, those with elevated CRP enjoy a poor prognosis (Hancox *et al.*, 2016). IL-8 is an essential inflammatory factor with high biological activity and can reflect the pathophysiological process after mycoplasma pneumoniae infection (Ding *et al.*, 2020). IL-6, a reactive protein in acute phase, originates from a wide range of sources, shows early increase with wide amplitude after bacterial infection, and demonstrates high sensitivity to infection (Cui *et al.*, 2017). IL-8, IL-6, and CRP, the three common indicators reflecting infection, can be used in combination for the diagnosis and differential diagnosis of acute infectious diseases. The results of this study showed that the levels of IL-8, IL-6 and CRP in each group were significantly reduced after treatment, and the reduction in the combination group was the most evident, indicating that erythromycin combined with azithromycin in the treatment of mycoplasma pneumonia can help reduce the level of inflammation in patients. Moreover, the present study revealed that inflammatory factors and pulmonary function indicators are independent influencing factors of ineffective treatment. Once again, it shows that erythromycin sequential therapy combined with azithromycin can effectively shorten the treatment period and greatly improve the treatment efficiency of children. As is known, adverse drug reactions adversely affect children physical and mental health and also delay disease progression.

CONCLUSION

In summary, the findings of this study show that mycoplasma pneumonia children using a combination of erythromycin sequential therapy and azithromycin produces significant improvement in effectiveness in clinical settings, with respect to inhibiting inflammatory reactions, controlling the disease in a timely manner, improving lung function, and resulting in fewer adverse reactions.

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