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Original Article

Human immunoglobulin in combination with antimicrobial agents enhances the treatment efficacy and reduces inflammatory response in children with severe pneumonia

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Abstract: Objective: To investigate the efficacy of human immunoglobulin combined with antibiotics in treating severe pediatric pneumonia. Methods: A retrospective analysis was performed on 210 pediatric patients with severe pneumonia admitted to the Department of Neonatology of Cangzhou Central Hospital from April 2019 to October 2022. Patients were divided into two groups (the observation group and the control group) based on the administration of human immunoglobulin. Clinical indexes of both groups before and after treatment were analyzed to determine the therapeutic effect of different treatment methods on pediatric severe pneumonia. Results: The durations of cough, fever, pulmonary rales, and lung shadow, and hospitalization time in the observation group were significantly shorter than those in the control group (all $P<0.05$). The total clinical effective rate in the observation group was significantly higher than that in the control group ($P<0.05$). Levels of inflammatory factors (IL-6, IL-8 and hsCRP) were decreased in both groups after treatment (all $P<0.05$), and were lower in the observation group compared with the control group after treatment (all $P<0.05$). The serum levels of IgA, IgG and IgM after five days of intervention were obviously higher than those before intervention in the observation group (all $P<0.05$), but the serum levels of IL-4, INF-γ and INF-γ/IL-4 were obviously lower (all $P<0.05$). The total incidence of adverse reactions between two groups after intervention was not statistically different ($P<0.05$). Conclusion: The combination of human immunoglobulin and antibiotics for the treatment of pediatric severe pneumonia is beneficial, because it improves efficacy, boosts the immune system, and reduces inflammation.

Keywords: Severe pneumonia, human immunoglobulin, immune function, inflammatory response

Introduction

Severe pneumonia is a specific type of pneumonia with a persistent and widespread disease burden [1, 2]. Children with severe pneumonia develop high fever, moderate to severe systemic symptoms, and an increased risk of damage to other organs. Mycoplasma pneumonia is caused by Mycoplasma, a common bacterial pathogen associated with a variety of clinical manifestations (upper respiratory tract infection and pneumonia). Mycoplasma pneumonia often occurs in the community, mostly in autumn and winter, with sporadic cases in other seasons, especially among school-age children and young adults [3, 4]. Mycoplasma pneumoniae pneumonia (MPP) is the most common community-acquired pneumonia (CAP) in children aged 5 or older in China [5]. Early detection of severe and critical cases, rational treatment, and avoidance of death and sequelae are the core and key issues in the management of MPP.

The pathogenesis of MPP has not been fully elucidated, but there are currently two main mechanisms [6, 7]: direct damage by MP and abnormal immune response of the host. Abnormal host immune responses to MP infection can lead to immune damage in the lung and extrapulmonary tissues through multiple pathways, including autoimmune reactions, allergic reactions, and immune complex formation. Abnormal host immune responses play an impor-

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tant role in the development of SMPP, FMPP and extrapulmonary complications and lead to clinical and imaging diversity of MPP [8].

In clinical practice, the treatment of pediatric severe pneumonia is complex and conventional antibiotic therapy is not effective. The occurrence of severe pneumonia is associated with factors such as susceptibility, immune insufficiency, and weak resistance [9-12]. Immunoglobulins are immune agents extracted from plasma that, when administered intravenously, neutralize pathogenic bacteria and modulate the immune and inflammatory response in patients with infectious diseases [13, 14].

Immunoglobulin combined with antimicrobial agents for the treatment of severe mycoplasma pneumonia has been studied more frequently [15, 16]. In order to clarify the value of human immunoglobulin in the treatment of severe mycoplasma pneumonia, this study specifically analyzed the efficacy of human immunoglobulin combined with antibiotics in the treatment of severe mycoplasma pneumonia in pediatric patients and its effects on immune function and inflammatory response.

Materials and methods

Case selection

Data of 210 children diagnosed with severe mycoplasma pneumonia treated in Cangzhou Central Hospital from April 2019 to October 2022 were retrospectively selected and grouped into two groups according to the treatment regimen. A total of 105 patients treated with azithromycin alone were assigned to the control group, and the other 105 patients treated with human immunoglobulin combined with azithromycin were assigned to the observation group. This study was approved by the Medical Ethics Committee of Cangzhou Central Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with persistent high fever for more than 5 days or fever for more than 7 days with no tendency of decreasing peak temperature. (2) Patients with wheezing, shortness of breath, dyspnea, chest pain and hemoptysis. These manifestations are associated with severe lesions, combined with plastic bronchitis, asthma attacks, pleural effusions and pulmonary embolism. (3) Patients who presented extra-pulmonary complications, but did not meet the criteria for critical illness. (4) Patients with finger pulse oxygen saturation less than 0.93 on air inhalation at rest. (5) Patients with any of following image manifestations: ① uniform-density mass lesions in more than 2/3 of a single lung lobe, or dense mass lesions in 2 or more lobes (regardless of the size of the area involved), which may be accompanied by moderate to massive pleural effusion or limited manifestations of fine bronchiectasis; ② diffuse single lung with manifestations of fine bronchiectasis, which may be combined with bronchiectasis and mucus plug formation leading to pulmonary atelectasis. (6) Progressive worsening of clinical symptoms, with imaging showing more than 50% progression of lesion extent within 24-48 h. (7) The guardians agreed to all treatment plans and signed the informed consent.

Exclusion criteria: (1) Children who were allergic to azithromycin or human immunoglobulin. (2) Children with a history of aspiration or aspiration pneumonia. (3) Children with immunocompromising or chronic medical conditions that predispose to severe or recurrent pneumonia (e.g., immunodeficiency, chronic corticosteroid use, chronic lung disease, malignancy, sickle cell disease, congenital heart disease, patients dependent on tracheostomy, and neuromuscular disorders impacting respiration). (4) Patients with incomplete medical records.

Treatment program

Children in both groups were treated with oxygen inhalation, cough suppressants and antipyretics, and the control group was given azithromycin anti-infection treatment: intravenous azithromycin administration (Shandong Luoxin Pharmaceutical Group Co., Ltd.; specification: 0.125 g × 1 bottle) 10 mg/(kg-d) for 5 days, followed by an equal amount of azithromycin oral solution (Shandong Luoxin Pharmaceutical Group Co., Ltd.; specification: 0.1 g × 4 sachets/times: 0.1 g × 4 bags/box) once per day for 5 consecutive days after the body temperature was normalized. In the observation group, human immunoglobulin (Hualan Bioengineering Pharmaceutical Co.; specification: 2.5 g (5%, 50 ml)) was added through intravenous drip, 1 time/d for 5 days.

Data collection

Demographic and clinical information, such as hs-C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), immunoglobulin A

Table 1. Comparison of general information between the two groups

Variables	Control (n=105)	Observation (n=105)	t/χ^2	*p*-value
Age	7.1±1.9	7.3±2.3	1.312	0.322
Gender				
Male	45 (42.86%)	50 (47.62%)	0.308	0.579
Female	60 (57.14%)	55 (52.38%)		
Course of disease (days)	8.84±1.77	8.39±1.67	0.134	0.066
Body temperature	39.66±0.42	39.22±0.32	0.342	0.087
Body mass index	18.87±0.22	18.46±0.32	0.214	0.079
Clinical symptoms				
Fever	100 (95.24%)	103 (98.1%)	0.312	0.096
Dyspnea	68 (64.76%)	78 (74.29%)	0.229	0.078
Hypotension	54 (51.43%)	68 (64.76%)	0.331	0.068
Shock	89 (84.76%)	79 (74.24%)	0.412	0.053
Cough	98 (93.33%)	101 (96.19%)	0.342	0.056
Bellyache	78 (74.29%)	83 (79.05%)	0.442	0.059
Myocarditis	59 (56.19%)	54 (51.43%)	0.487	0.055

(IgA) (Add& Read Human IgG Kit, Vazyme, China), immunoglobulin G (IgG) (Add& Read Human IgG Kit, Vazyme, China), immunoglobulin M (IgM) (IgM ELISA Kit, Abnova) and interferon gamma (IFN-γ) were retrospectively collected from all patients by reviewing their electronic medical records. During the hospitalization, adverse reactions and symptoms of patients were obtained, including nausea, vomit, rash, abdominal pain, diarrhea and so on.

The clinical efficacy of the two groups was compared. Markedly effective: After therapy, the chest CT scan showed that the lungs of the patient were normal; Effective: After therapy, the patient's clinical symptoms were alleviated to a certain extent, and the chest CT scan results showed that the patient's lungs had alleviated to a certain extent; Ineffective: After therapy, the patient's clinical symptoms and chest CT scans results were not changed. Total effective treatment rate = [(number of cases with markedly effective + cases of effective)/ the total number of patients] × 100%.

Detection of immune and inflammatory biomarkers

Three to five milliliters of venous blood were collected before and after treatment and the serum was centrifuged. The enzyme-linked immunosorbent assay (ELISA) was used to determine immunoglobulin A (IgA) (Add& Read Human IgG Kit, Vazyme, China), immunoglobulin G (IgG) (Add& Read Human IgG Kit, Vazyme, China), immunoglobulin M (IgM) (IgM ELISA Kit, Abnova), interferon gamma (IFN-γ) (Human IFN-γ ELISA Kit, Beyotime, China), interleukin-4 (IL-4) (Human IL-4 ELISA Kit, Beyotime, China), hypersensitive C-reactive protein (hs-CRP) (Human hs-CRP ELISA Kit, WELLBI, China), interleukin-6 (IL-6) (CSB-E04638h, CUSABIO, Wuhan, China) and interleukin-8 (IL-8) (CSB-E04641h, CUSABIO, Wuhan, China). All ELISA experiments were measured in a Thermo Fisher Microplate Reader.

Statistical analysis

SPSS 20.0 software (Chicago SPSS Co., Ltd.) was used for statistical analysis. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as the number of cases and percentages (%). The independent t-test was used for comparison between the two groups, and the paired t-test was used for comparison of the same group at different time periods, and the results were expressed by t. The categorical variables were compared by chi-square test. $P<0.05$ indicated a significant difference.

Results

Basic data

Table 1 shows the characteristics of the patients in the two groups. There were 105 chil-

Table 2. Comparison of clinical therapeutic effect between the two groups

Therapeutic effect	Observation group (n=105)	Control group (n=105)	χ^2	*P*
Significant effective	34 (32.38%)	19 (18.10%)	7.368	0.008
Effective	54 (51.43%)	46 (43.81%)	9.837	0.022
Ineffective	11 (10.48%)	34 (32.38%)	4.161	0.013
Total effective rate	88 (83.81%)	67 (63.81%)	6.478	0.012
t	4.957	5.632	-	-
P	0.062	0.071	-	-

dren in the control group with a mean age of 7.14±1.92 years. There were 105 children in the observation group with a mean age of 7.3±2.3 years. The two groups were comparable in terms of sex, age, course of disease, body temperature, BMI and clinical symptoms (all P>0.05).

Comparison of clinical therapeutic effect between the two groups

As shown in **Table 2**, the total effective rate in the observation group was 83.8% (88/105), which was significantly higher than the 63.8% in control group (P<0.05).

Comparison of serum levels of immune factors in observation group before and five days after intervention

The serum levels of IgA, IgG and IgM after five days of intervention were obviously higher than those before intervention in the observation group (all P<0.05). On the other hand, the serum levels of IL-4, INF-γ and INF-γ/IL-4 after five days of intervention were obviously lower than those before intervention in the observation group (all P<0.05, **Figure 1**).

Comparison of serum levels of inflammatory factors between the two groups

There was no significant difference in inflammatory factors (IL-6, IL-8 and hsCRP) between the two groups before treatment (P>0.05). After five days of intervention, the levels of above indicators were obviously decreased in both groups, and the levels in the observation group were significantly lower than those in the control group after intervention (all P<0.05, **Figure 2**).

Comparison of adverse reactions between the two groups

There was no significant difference in the incidence of nausea, vomiting, rash, abdominal pain and diarrhea between the two groups after intervention (all P>0.05, **Table 3**).

Comparison of duration of clinical symptoms and hospitalization time between the two groups

The durations of cough, fever, pulmonary rales, lung shadow, and hospitalization time in the observation group were significantly shorter than those in the control group (all P<0.05), as shown in **Table 4**.

Discussion

Immunocompromise is closely associated with the development of severe pneumonia, and enhancing immune function is a treatment for pneumonia that has been increasingly recognized in recent studies [17-19]. Human immunoglobulins are antibodies extracted from plasma that play an important role in the primary immune response [20-23]. In addition, immunoglobulins can impede apoptosis of immune cells and enhance immune function [24, 25]. In our study, human immunoglobulin was additionally added to conventional antibiotics for the treatment of pediatric severe pneumonia, and the overall effective rate of children in the observation group was higher than that of the control group. The cough relief time and temperature recovery time were shorter in the observation group than those in the control group. These results suggest that human immunoglobulin can improve the efficacy and clinical symptoms in the treatment of pediatric severe pneumonia.

This study further analyzed the changes in immune biomarkers before and after the use of human immunoglobulins. IgA, IgG and IgM are immunoglobulins involved in humoral immune responses and are able to recognize and bind

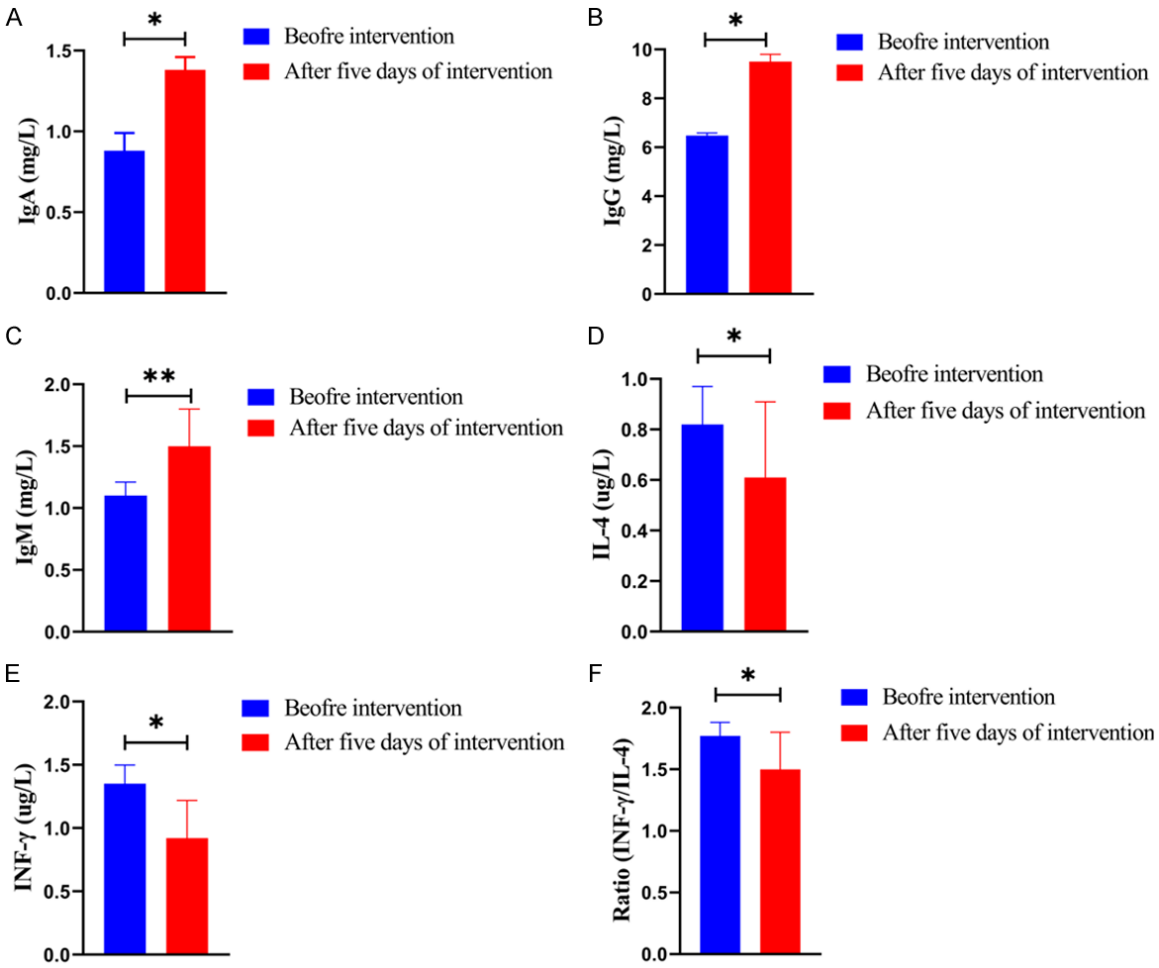

Figure 1. Comparison of immune biomarkers in the observation group before and five days after intervention. A: Comparison of serum levels of IgA before and after five days of intervention; B: Comparison of serum levels of IgG before and after five days of intervention; C: Comparison of serum levels of IgM before and after five days of intervention; D: Comparison of serum levels of IL-4 before and after five days of intervention; E: Comparison of serum levels of INF-γ before and after five days of intervention; F: Comparison of serum levels of INF-γ/IL-4 before and after five days of intervention; Note: Compared with before intervention, $^{*}P<0.05$, $^{**}P<0.01$. Note: IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IL-4: Interleukin-4; INF-γ: Interferon gamma.

to pathogens and kill them through immune responses. When immunoglobulins are not sufficient, pathogens cannot be destroyed in time after their invasion. During persistent pathogen infection, the secretion of immunoglobulins is further suppressed, which is detrimental to pathogen clearance [26, 27]. Analysis of immunoglobulins showed that serum IgA, IgG and IgM levels increased significantly in both groups after treatment. The trend of increasing immunoglobulins after treatment was more pronounced in the observation group than that in the control group. This indicates that human immunoglobulin treatment for pediatric severe pneumonia can increase immunoglobulin concentrations and improve the humoral immune system.

The disruption of Th1/Th2 balance in the body is an important mechanism of decreased immunoglobulin secretion caused by pathogenic infections [28, 29]. The shift of Th1 to Th2 in mycoplasma pneumonia favors a compensatory enhancement of humoral immunity, as evidenced by increased secretion of IFN-γ and IL-4, with a more pronounced increase in IL-4 and a decrease in the IFN-γ/IL-4 ratio [30]. The serum levels of IL-4, INF-γ and INF-γ/IL-4 after five days of intervention were obviously lower than those before intervention in the observation group. This study suggests that the use of human immunoglobulin in the treatment of pediatric severe pneumonia can regulate the Th1/Th2 balance and avoid excessive activation of Th2.

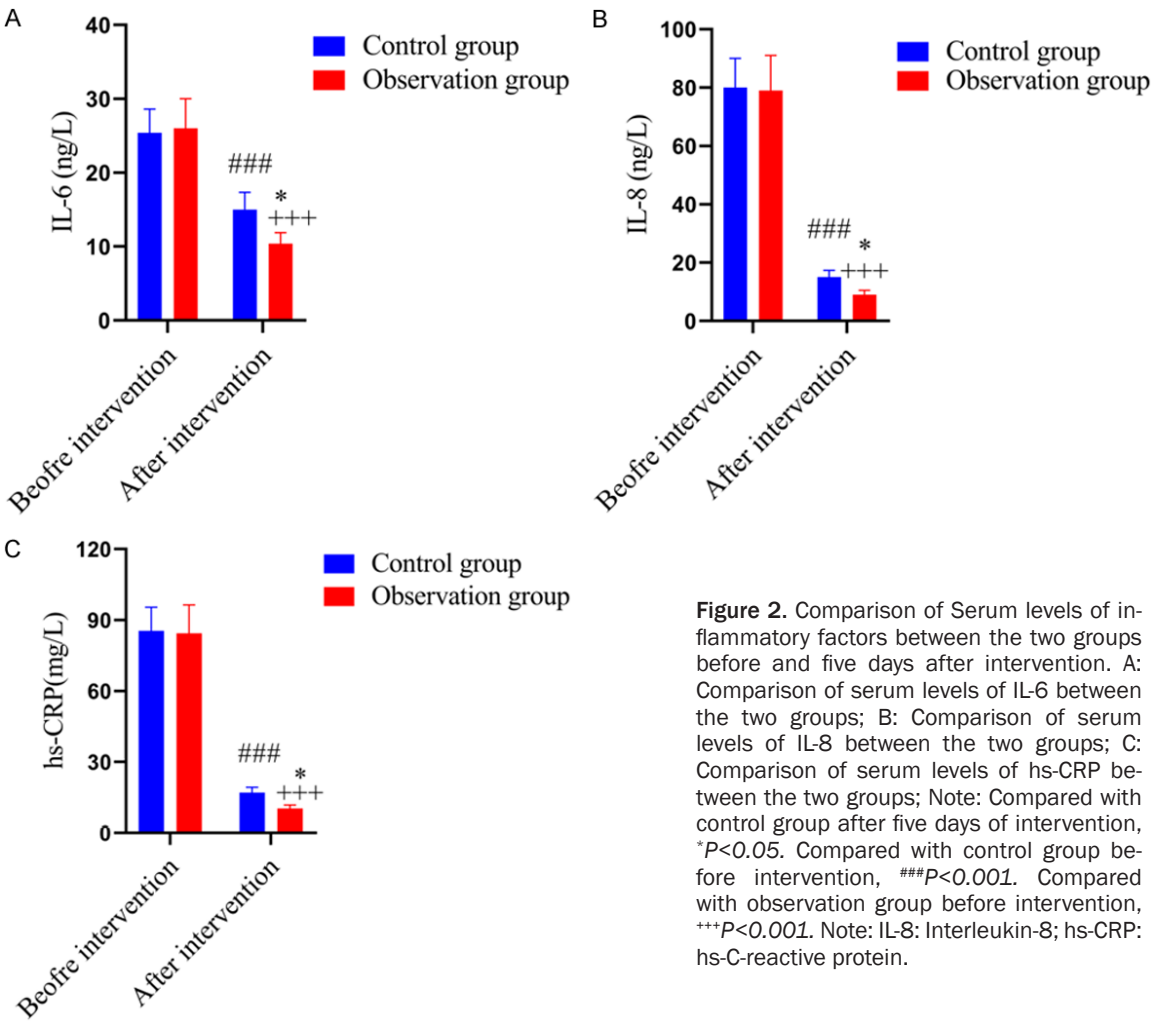

Figure 2. Comparison of Serum levels of inflammatory factors between the two groups before and five days after intervention. A: Comparison of serum levels of IL-6 between the two groups; B: Comparison of serum levels of IL-8 between the two groups; C: Comparison of serum levels of hs-CRP between the two groups; Note: Compared with control group after five days of intervention, $^{*}P<0.05$. Compared with control group before intervention, $^{\#\#\#}P<0.001$. Compared with observation group before intervention, $^{+++}P<0.001$. Note: IL-8: Interleukin-8; hs-CRP: hs-C-reactive protein.

Table 3. Comparison of adverse reactions between the two groups

Adverse reactions	Observation (n=105)	Control (n=105)	χ^2	*P*
Nausea	17 (16.19%)	10 (9.52%)	7.253	0.743
Vomit	21 (20.00%)	32 (30.48%)	6.378	0.158
Rash	20 (19.05%)	31 (29.52%)	3.721	0.842
Abdominal pain	34 (32.38%)	33 (31.43%)	4.161	0.151
Diarrhea	15 (14.29%)	7 (6.67%)	9.837	0.482
Total incidence	38 (36.19%)	46 (43.81%)	6.693	0.232

Table 4. Comparison of duration of clinical symptoms and hospitalization time between the two groups

Clinical symptoms and hospitalization time	Observation (n=105)	Control (n=105)	t	*P*
The duration of cough	6.20±0.90	8.02±0.95	1.702	0.041
The duration of fever	5.48±0.84	7.93±0.94	2.101	0.031
The duration of pulmonary rales	6.02±1.25	7.67±1.52	2.032	0.026
The duration of lung shadow	8.87±2.31	11.68±2.48	4.161	0.021
Hospitalization time	7.24±3.22	12.97±4.47	6.837	0.012

Persistent mycoplasma infection during mycoplasma pneumonia can activate the inflammatory response *in vivo*. The activation of the inflammatory response in children with severe pneumonia is intense, and various inflammatory mediators are released in a cascade. hs-CRP is an acute temporal protein synthesized by hepatocytes, and pro-inflammatory factors can stimulate hepatocytes to secrete large amounts of hs-CRP during the activation of inflammatory response [31-37]. The results of this study showed that the levels of IL-6, IL-8 and hsCRP in the peripheral blood of both groups were significantly lower than those before treatment, and the levels in the observation group were significantly lower than those in the control group. This result suggests that human immunoglobulin can significantly suppress the inflammatory response in pediatric severe pneumonia.

Although our study illustrates the effectiveness of immunoglobulins in the treatment of severe mycoplasma pneumonia in children, there are still some limitations. This is a retrospective single-center study with small sample size and only focused on mycoplasma pneumonia. In future studies, we will conduct a number of prospective studies and expand the types of disease.

In conclusion, human immunoglobulin combined with antibiotics for the treatment of pediatric severe pneumonia can improve the efficacy, shorten the duration of clinical symptoms, improve immune function, and suppress the inflammatory response.

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Disclosure of conflict of interest

None.

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