Clinical characteristics of refractory *Mycoplasma pneumoniae* pneumonia in children treated with glucocorticoid pulse therapy

Zhenli Zhu  
Tianjin Medical University

Tongqiang Zhang  
Tianjin Agricultural University

Wei Guo  
Tianjin Children's Hospital

Yaoyao Ling  
Tianjin Medical University

Jiao Tian  
Tianjin Medical University

**Yongsheng Xu**  (✉ 1139350425@qq.com)  
Tianjin Children's Hospital  https://orcid.org/0000-0002-5182-2819

**Research article**

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Abstract

Objective: To observe the effect of corticosteroids in the treatment of children with refractory Mycoplasma pneumoniae pneumonia (RMPP) under different doses, to summarize the clinical characteristics of children treated with glucocorticoid pulse therapy.

Methods: The clinical data of 125 children with RMPP hospitalized in Tianjin Children's Hospital from September 2018 to October 2019 were retrospectively analyzed. They were divided into two groups according to the dose of hormone. Group I was given conventional dose methylprednisolone 2mg/kg/day (<200mg/day) (n=81), and group II was treated with methylprednisolone pulse therapy ≥200mg/day (n=44). Compare the clinical manifestations, laboratory findings, and imaging between the two groups of children, and use meaningful related indicators as ROC curves to find reference indicators for pulse therapy.

Results: (1) The age and weight of the group II were greater than the group I (P<0.05). (2) The symptoms of group II were more serious than group I, with higher incidence of hypoxemia, longer fever, longer hospital stays, higher incidence of extrapulmonary complications, and more severe radiological findings (P<0.05). (3) The more severe the disease was, the higher hormone amount use rate of gamma globulin use rate of bronchoscopy, and incidence of plastic bronchitis (P<0.05) were. (4) WBC, CRP, LDH, FER, D-D dimer, APTT, TT, PCT, IL-6 and the percentage of neutrophils in peripheral blood in Group II were higher than those in Group I (P<0.05). Moreover, the lymphocyte percentage level in group II was lower than that in group I (P<0.05). (5) In ROC curve analysis, CRP, LDH, FER, and neutrophils of leukocyte classification were independent related factors that could be used as valuable predictors of methylprednisolone pulse therapy for RMPP in children. The cut-off values were CRP 44.45 mg/L, LDH 590 IU/L, FER 411 ng/L, and neutrophils in leukocyte classification were 73.75%, respectively.

Conclusions: Conventional dose methylprednisolone can improve the clinical symptoms and imaging findings of most children with RMPP rapidly. However, CRP 44.45 mg/L, LDH 590 IU/L, FER 411 ng/L, neutrophil 73.75%, lung consolidation and pleural effusion were found in RMPP patients, which should be treated with pulse dose of methylprednisolone in time to reduce the incidence of severe RMPP and the occurrence of severe sequelae.

Introduction

Mycoplasma pneumoniae (MP) is one of the major pathogeneses of community-acquired pneumonia (CAP) in children. Mycoplasma pneumoniae pneumonia (MPP) is usually considered as a benign and self-limiting disease. However, it has been found in clinical practice that some children still progress to refractory Mycoplasma pneumoniae pneumonia (RMPP) after being treated with sufficient and long-term macrolide antibiotics in timely, which often leads to serious internal and external pulmonary complications, such as pulmonary necrosis and pleural effusion, which may not only be difficult to treat and costing, but also leave sequelae such as bronchiectasis, atelectasis, necrotizing pneumonia and
bronchiolitis obliterans\cite{3-7}, thus affect the quality of life. Over-immune response of host plays an important role in the development of RMPP\cite{8,9}. Studies have confirmed the effectiveness of corticosteroids in the treatment of RMPP\cite{2,10,11}. Glucocorticoids are effective in the treatment of severe MPP by down-regulating the cell-mediated immune response associated with lung injury during infection\cite{12-15}. Therefore, on the basis of adequate anti-infective treatment, immunotherapy, especially the combination therapy of glucocorticoids, has attracted more and more attention\cite{16,17}. It is important for clinicians to identify severe RMPP as early as possible and give administer pulse dose hormone therapy. So, Retrospective analysis was performed on 125 children with RMPP hospitalized in our hospital from September 2018 to October 2019, to observe different doses of glucocorticoid in the treatment of children with RMPP. The clinical manifestations, laboratory data and imaging findings of all children were compared to summarize the clinical characteristics of children in glucocorticoid pulse treatment group, in order to provide basis for pulse therapy of RMPP.

**Methods**

**Research Objects**

**Clinical information**

This study selected 125 children with RMPP who were treated with different doses of methylprednisolone at Tianjin Children's Hospital from September 2018 to October 2019 and divided them into two groups. Group I was given routine dose of methylprednisolone 2mg/kg/day (< 200mg/day) and a total of 81 cases were included. Group II was given pulse dose of methylprednisolone $\geq$ 200mg/day, and a total of 44 cases were included.

**Diagnostic criteria**

**MPP diagnostic criteria**\cite{18}

(1) Symptoms and signs of pneumonia showed on admission, including fever, cough, abnormal lung auscultation and so on; (2) Chest imaging indicates pneumonia; (3) Positive results for serologic test. Included patients underwent anti-MP IgM titrations twice, both at the time of admission and upon discharge. Patients who showed either a seroconversion (negative to positive), or four-fold or greater increase in IgM titers and who had both symptoms with $\geq$1:640 high titers. The diagnosis of RMPP was based on the presence of persistent fever and clinical as well as radiological deterioration after azithromycin treatment for 7 days or longer. Clinical and radiological deterioration is described as follows\cite{10,17}; aggravation of clinical signs is characterized by persistent fever, severe cough, dyspnea, etc. Radiological aggravation showed enlargement of pulmonary lesions, increased density, pleural effusion, and even necrotizing pneumonia and lung abscess.

**Inclusion criteria**
(1) Meet the diagnostic criteria of MPP; (2) Meet the definition of RMPP; (3) Age ≤ 16 years old.

**Exclusion criteria**

- 1) Patients who had a history of tuberculosis, bronchiectasis, or lung tumors;
- 2) Patients who had diseases such as severe malnutrition, unconsciousness, chronic cardiac and pulmonary disease, congenital disease, or immunodeficiency;
- 3) Patients who received corticosteroids before admission;
- 4) Patients who were discharged within 8 hours after admission.

**Hormone grouping**

Conventional dose corticosteroid use was defined as intravenous infusion of methylprednisolone 2mg/kg/day (<200mg/day) (or an equivalent dose of dexamethasone, hydrocortisone, prednisolone or betamethasone), and pulse therapy ≥ 200 mg/day methylprednisolone (or an equivalent dose of dexamethasone, hydrocortisone, prednisolone or betamethasone).

**Grouping**

All selected children were treated with routine dose of methylprednisolone intravenously within 48-72 hours after admission. According to changes in body temperature, children with RMPP were divided into conventional dose group and pulse dose group:

1) Conventional dose group: after given the initial of methylprednisolone 2mg/kg/day (<200mg/day), their body temperature returned to normal within 24 to 48 hours, their imaging abnormality gradually improved, CRP returned to normal, and there was no recurrence in the process of hormone withdrawal.

2) Pulse therapy: Initially given methylprednisolone 2mg/kg/day, there is no significant decrease in heat peak within 24 to 48h after treatment (<1℃), and after 72h there was still high fever. Moreover, their imaging abnormality do not improve or even progress after given methylprednisolone ≥ 200mg/day their body temperature returned to normal within 24 to 48h.

**Data collection**

Demographic, clinical information, laboratory data and radiological findings were retrospectively collected from all children who were included in the study. Nasopharyngeal aspirate/swab specimens were routinely collected within 24 hours of admission. Respiratory specimens were bacterially cultured and ran virus test by using direct immunofluorescence assays, and tested with MP of PCR. Peripheral blood samples were collected upon admission for the determination of the complete blood count, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCT), interleukin (IL)-6, lactic acid (La), ferritin (Fer), d-dimer, fibrinogen (Fg), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and specific antibody to MP. Blood cultures were also performed on admission. All patients underwent imaging studies before admission or during hospitalization. During the hospitalization, we also evaluated the extra-pulmonary complications (liver function abnormalities, myocarditis, encephalitis, rash, proteinuria, hemolytic anemia and arthritis) of patients. Hypoxia was defined as any recorded oxygen saturation of <92% by pulse oximetry, measured in indoor air.
Observation indexes

Clinical features (sex, age, duration of fever, duration of hospitalization, complications, hypoxia, etc.), radiological findings and laboratory data.

Ethics

The study was approved by the ethics committee of the Tianjin Children's Hospital. And the data from patients were analyzed anonymously.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 22.0). Normal distribution data were expressed as mean ± SD (x ± s). Independent-Samples T-test or One-way ANOVA was used to process these data. The skewed distribution data were presented as the median values (P25, P75), and comparisons were made by the Mann-Whitney U-test. Chi-squared tests were used to compare numerical data, which was presented as rate or constituent ratio. Meanwhile, we use the laboratory indicators with significant differences as independent related risk factors to make the ROC curve, and use the area under the ROC curve (AUC) to reflect the accuracy of the diagnostic test. The value range of AUC is 0.5–1, AUC=0.5 means a completely worthless diagnosis; 0.5<AUC≤0.7 means low diagnostic accuracy; 0.7<AUC≤0.9 indicates that the diagnostic accuracy is moderate; 0.9<AUC<1 means higher diagnostic accuracy; AUC=1 indicates a perfectly ideal diagnosis. Take the point closest to the upper left corner of the ROC curve, which has the largest sum of sensitivity and specificity, as the optimal value of prediction.

Results

General information of patients

This study included 125 children who were diagnosed with RMPP in Tianjin Children's Hospital from September 2018 to October 2019. All patients met the diagnostic criteria. All patients were treated with macrolide antibiotics against infection. All patients were previously healthy without underlying disease. Children were divided into two groups according to glucocorticoid dose. The age distribution of the subjects is shown in Figure 1. The 81 patients in group I (36 females, 45 males) had the median age of 6.00±4.00–7.50±, and the median weight of 20.4±16.4–28.9±kg; The 44 patients in group II (22 females, 22 males) had the median age of 7.00±6.00–9.75±, and the median weight of 27.2±20.0–33.5±kg, which was shown in Table 1. No difference in gender distribution was found between the groups(P>0.05). The age and weight of the two groups were of statistically significance (P<0.05).

Clinical information of patients
There were no statistically significant differences in fever and cough among the two groups (P>0.05). The incidence of hypoxemia was 63.6% in group II, and 7.41% in group I, with a significant difference (P<0.05) (Table 1). The incidence of respiratory failure was 4.55% in group II, 0% in group I, with a statistically significant (P<0.05). Concerning the clinical course, we found that the length of fever was 13–11–15 days in group II, 11–8–13 days in group I, with a statistically significant difference (P<0.05). The days of fever before hospitalization was 6–4–7 days in group II, and 7–5–8 days in group I, with no statistically significant difference (P>0.05). The days of fever after hormone administration in II group and in group I were 5.5–3–7 days and 1–1–2 days respectively, the difference was statistically significant. The length of stay was 13.5–11.3–16 days in group II, and 8–7–10 days in group I, which did not reach statistical significance (P<0.05). The incidence of extrapulmonary complications was 75.0% in group II, and 22.2% in group I with a significant difference (P<0.05). The incidence of pulmonary embolism in group II was 4.55%, and was 2.47% in group I, and the difference was not statistically significant (P > 0.05).

**Treatment of patients**

All patients were treated with antibiotics. The hormone dosage was 10 (8.5, 10) mg/kg/day in group II and 2 (1.5, 2) mg/kg/day in group I, with statistically significant differences(P<0.05). The use rate of gamma globulin was 38.6% in group II, and 11.1% in group I, and the difference was statistically significant (P <0.05). The use rate of bronchoscopy was 93.2% in group II, and 70.4% in group I, with a statistically significant (P<0.05). The incidence of plastic bronchitis was 65.9% in group II, and 17.3% in group I, and the difference was statistically significant (P<0.05).

### Table 1. Clinical characteristic

| Clinical information                                      | Group I | Group II | P-value |
|----------------------------------------------------------|---------|----------|---------|
| General information                                       |         |          |         |
| Sex (female/male)                                        | 36/45   | 22/22    | 0.552   |
| Age, years                                               | 6.00(4.00,7.50) | 7.00(6.00,9.75) | 0.031   |
| Weight, kg                                               | 20.46(16.42,28.90) | 27.22(20.00,33.55) | 0.002   |
| Clinical presentation, n (%), fever                       | 81/100% | 44/100%  | 1.00    |
| Cough                                                    | 75/92.6% | 43/97.7% | 0.891   |
| Hypoxemia in group II, n (%), respiratory failure        | 67/74.1% | 28/63.6% | 0.000   |
| Extra-pulmonary complications in group II, n (%), fever  | 18/22.2% | 33/75.0% | 0.007   |
| Thromboembolism in group II, n (%)                        | 28/24.7% | 26/22.4% | 0.613   |
| Total fever duration, days                               | 11/8/13 | 13/11/15 | 0.000   |
| Preadmission fever duration, days                        | 7/5/8   | 6/4/7    | 0.329   |
| Fever duration at the time of CS treatment, days         | 10/12/2 | 5.5/3/7 | 0.000   |
| Length of stay, days                                     | 8/7/10c | 13.5/11.3/16 | 0.000 |
| Management                                               |         |          |         |
| Hormone dose, mg/kg/day                                  | 20/1.5/20 | 100/8.5/10 | 0.000 |
| Gamma globulin, n (%)                                    | 9/11.1% | 17/38.6% | 0.000   |
| Bronchoscopy, n (%)                                      | 57/7.0% | 41/93.2% | 0.000   |
| Plastic bronchitis, n (%)                                | 14/17.3% | 29/65.9% | 0.000   |

Data are presented as number (percentage), median (25th-75th percentile).

**Laboratory of patients**
Laboratory data in two groups of patients were summarized in Tables 2. The values of Fg, PT, PLT, La, ALT and AST did not differ significantly between the two groups. (P >0.05). The levels of WBC, CRP, LDH, FER, D-dimer, APTT, TT, PCT, IL-6 and the percentage of peripheral neutrophils in children between 2 groups showed a gradual upward trend, with a significant difference (P<0.05).

| Laboratory information     | Group I:81 | Group II:44 | P-value |
|----------------------------|------------|-------------|---------|
| White blood cell (×10^9/L) | 9.00(7.5011.20) | 11.39(9.0114.80) | 0.001   |
| Neutrophil,%               | 66.00(48.073.75) | 81.68(76.3087.00) | 0.000   |
| Lymphocytes,%              | 25.51(16.8540.00) | 12.1(8.2515.0) | 0.000   |
| CRP, mg/L                  | 36.9(12.567.2) | 69.0(54.0108) | 0.000   |
| LDLH, IU/L                 | 456(345586) | 594(397776) | 0.007   |
| FER, ng/L                  | 255(126345) | 543(321828) | 0.000   |
| D-D, mg/L                  | 0.4(0.211.0) | 1.15(0.303.28) | 0.011   |
| Fg, g/l                    | 3.70(3.314.37) | 3.84(3.304.72) | 0.307   |
| PT                         | 11.9(11.4112.4) | 11.7(11.0112.3) | 0.147   |
| APTT                       | 30.8(27.834.3) | 26.4(24.030.4) | 0.000   |
| TT                         | 16.3(15.5117.2) | 17.1(16.2117.8) | 0.002   |
| PLT                        | 338(269448) | 294(225408) | 0.054   |
| PCT, ng/ml                 | 0.18(0.100.37) | 0.33(0.170.55) | 0.007   |
| IL-6, pg/ml                | 26.0(14.845.9) | 46.7(25.11100.9) | 0.001   |
| La, mmol/L                 | 2.81(2.363.36) | 2.86(2.353.50) | 0.781   |
| AST, U/L                   | 35(2753) | 39(2953) | 0.460   |
| ALT, U/L                   | 17(1223) | 21(1225) | 0.094   |

Data are presented as number (percentage).

**Imaging findings of patients**

Radiological findings in two groups of patients were summarized in Tables 3. The difference in the incidence of atelectasis (25.0% versus 21.0%) and pleural thickening (68.2% versus 64.2%) did not reach statistical significance (P>0.05). And there were statistically significant differences between the two groups in the incidence of pulmonary complications, including pulmonary consolidation (93.2% versus 51.9%, P<0.05) and pleural effusion (45.5% versus 27.2%, P<0.05).

| Radiological features     | Group I:81 | Group II:44 | P-value |
|----------------------------|------------|-------------|---------|
| Pulmonary consolidation, n (%) | 42(51.9%) | 41(93.2%) | 0.000   |
| Pleural effusion, n (%)    | 22(27.2%) | 20(45.5%) | 0.039   |
| Lobar atelectasis, n (%)   | 17(21.0%) | 11(25.0%) | 0.607   |
| Pleural thickening, n (%)  | 52(64.2%) | 30(68.2%) | 0.654   |

Data are presented as number (percentage).

**Predictive values of the independent correlation factors of patients**

To explore the optimal values of laboratory date for groups, receiver operator characteristic (ROC) curves were made and the cut-off values with maximum sensitivities and specificities were determined. The
analysis of these ROC curves shows that CRP, LDH, FER, neutrophil percentage can be used to express the clinical features of children with RMPP treated with pulse dose (Table 4). When the cut-off values for CRP, LDH, FER, neutrophil percentage were set at 44.45 mg/L, 590 IU/L, 411 ng/L, 73.75 respectively, it is helpful to guide the use of pulse dose glucocorticoids in children with RMPP. The sensitivity and specificity were respectively 55.0% & 85.0%, 76.3% & 47.5%, 86.4% & 68.2%, and 75.0% & 90.0%.

Table 4 Predictive values of the independent correlation factors

| Independent factors | Cutoff value | Sensitivity | Specificity | AUC    | P-value | 95%CI       |
|---------------------|--------------|-------------|-------------|--------|---------|------------|
| Neutrophil, %       | 73.75        | 0.750       | 0.900       | 0.888  | 0.000   | 0.831-0.945|
| CRP, mg/L           | 44.45        | 0.550       | 0.850       | 0.736  | 0.000   | 0.648-0.825|
| LDH, IU/L           | 590.0        | 0.763       | 0.475       | 0.611  | 0.048   | 0.503-0.719|
| Fer, ng/L           | 411.0        | 0.864       | 0.682       | 0.814  | 0.000   | 0.736-0.892|

AUC: area under the ROC curve; Cut-off value: the value on the ROC curve is closest to the upper right to take maximum sensitivity and specificity;

P value: the AUC value of the independent factors compared to ROC curve reference value 0.5.

**Discussion**

Mycoplasma pneumoniae infection was the leading pathogen of CAP in children. It is traditionally assumed that MP infection was a benign process, but more and more severe cases have been reported in recent years [26-30]. Cases of RMPP were increasingly reported which displayed clinical and radiological progression after macrolide therapy for 7 days or longer [2, 17, 31]. Thus, it is essential for pediatricians to identify RMPP as early as possible, then give prompt therapy and prevent disease from progression. Studies [32, 33] have shown that more than 90% of Mycoplasma pneumoniae infections in China are caused by drug-resistant strains. However, the latest research results of Sun et al [34] showed that the important cause of MP resistance to macrolide antibiotics was not only the irregular use of antibiotics, but also was related to the epidemic genotype M4-5-7-2 of Mycoplasma pneumoniae. Through the comparison of genotypes and drug resistance between Chinese, American and Australian strains, it is reasonably explained from a new perspective that the high drug resistance rate in China and even in Asia is not all caused by the abuse of antibiotics, which is closely related to the regional differences in the epidemic genotypes of Mycoplasma pneumoniae [34]. Therefore, macrolides are still used in patients with MP in China. Only when macrolides are ineffective, antibiotics such as tetracyclines or fluoroquinolones can be used according to the condition [35-39]. Due to the influence of the pathogenesis, most of the RMPP will produce both intrapulmonary symptoms and extrapulmonary complications, which may involve the heart system, liver system, central nervous system, hematopoietic system and skin. The host’s excessive immune response plays an vital role in the development of RMPP disease [8, 9], such as cytokines (including interleukin-2, interleukin-5, interleukin-6, interleukin-8 and leukocytes-18). Overexpression and highly activated cells (including antigen presenting cells and T cells) mediated immune response etc. [40]. Glucocorticoids can be used to down-regulate the related cell-mediated immune response and play an effective role in severe cases of Mycoplasma pneumoniae infection [12-14]. Early control of lung injury caused by overactive immune response by non-specific
adaptive immune cells is essential for reducing the incidence of severe MPP and preventing disease progression. Since the severity of RMPP is related to the corresponding immune response, and the effect of GS is dose-dependent, higher doses may be needed in patients with severe pneumonia infected by MP\cite{4, 41, 42}.

A number of studies have suggested that humoral and cellular immune responses\cite{43, 44} contribute to the pathogenesis of MP infection, providing a theoretical basis for the application of immunosuppressive agents such as glucocorticoids in Mycoplasma pneumonia. Studies have shown that the addition of GCs on the basis of the conventional treatment has a definite effect on RMPP, which contributes to the control of the disease progression, the improvement of the condition and the reduction of sequelae\cite{10, 16}. So, it is very important for pediatricians to study the application of glucocorticoids in the treatment of RMPP\cite{2, 16, 45}. In this retrospective research, 125 patients with RMPP were enrolled. Among them, there are 81 cases in group I, and 44 cases in group II. The different clinical characteristics between the RMPP patients were compared. First of all, this study found that there was a statistical difference in age between group I and group II $6.00 \pm 4.00$ vs $7.50 \pm 7.00$ vs $6.00 \pm 9.75$ vs $P<0.05$, which was consistent with the previous reports\cite{11, 17}. Children's immune system develops with age, and is prone to excessive inflammatory reaction to MP, which may lead to the progression of RMPP. It was also found that the body weight of children in group II was higher than that in group I $27.2 \pm 20.0$ vs $33.5 \pm 20.4$ vs $16.4 \pm 28.9$ vs $P<0.05$. Secondly, higher incidence of hypoxemia, extra-pulmonary complications and plastic bronchitis were found in the group II than in the groups I ($P<0.05$). Moreover, the proportion of patients required oxygen therapy, gamma globulin and bronchoscopy in the group II was higher than that in the group I ($P<0.05$). The total fever days, hospital stay, fever days after hormone use and the dosage of corticosteroids in group II were significantly higher than those in group I ($P<0.05$). These results indicated that if RMPP is not treated effectively in time, the clinical course of disease may be prolonged and the disease may be aggravated. It also showed that with more severe of symptoms, there will be longer clinical course, greater hormone use, higher incidence of extrapulmonary complications, and higher incidence of plastic bronchitis. Additionally, our research also showed that higher incidence of pulmonary consolidation and pleural effusion were found in group II than in groups I ($P<0.05$). The diversification of imaging findings may be due to direct microbial effects and strong immune inflammatory response. Finally, the study also found that WBC, CRP, LDH, FER, D-D dimer, APTT, TT, PCT, IL-6, ALT and the percentage of neutrophils in peripheral blood were gradually increasing in both group I and group II ($P<0.05$).

In order to study the clinical features that may predict the severity of RMPP disease and guide the use of pulse doses of glucocorticoids, we used ROC curves to analyze statistically significant indicators. This study found that the area under the curve of four independent factors, including CRP, LDH, FER, leukocyte classification of neutrophils was above 0.6 in ROC curve analysis, indicating fair discriminative power. The optimal cutoff value for these four factors was 44.45 mg/L, 590 IU/L, 411 ng/L and 73.75%, respectively. We found that CRP 44.45 mg/L, LDH 590 IU/L, FER 411 ng/L, leukocyte classification neutrophil 73.75%, lung consolidation, pleural effusion may be an important clinical feature of pulse dose hormone use in RMPP patients. CRP is a gross biochemical index of inflammation and is used commonly
in the clinical setting. CRP reflected the acute severe systemic inflammatory reactions to MP infection, and was suggestive of a well-developed immune system. Liu et al. showed that the cutoff value of CRP for RMPP was 40mg/L. The cutoffs were less than that in our study. The main reason of which may be that our results were obtained from a small case series, and our study had more serious illnesses. In this study, the optimal cutoff point for CRP was 44.45mg/L, with a sensitivity of 55% and specificity of 85%. These indicate their clinical utility in identifying patients who are at high risk for RMPP. LDH was associated with many lung diseases, such as obstructive and interstitial lung diseases. Several studies also found that serum LDH was elevated in RMPP. In our study, we found that the area under the curve of LDH was 0.611 in ROC curve analysis, showing fair discriminative power. The optimal cutoff for LDH was 590IU/L, with 76.3% sensitivity and 47.5% specificity, which was higher than that of previous studies. The main reason may be that the condition of the children was more serious.

Ferritin represents not only iron reserves but also an inflammatory marker. When inflammation occurs, inflammatory factors act on the body and increase the production of ferritin in serum. At the same time, inflammatory factors cause degeneration, dissolution, and necrosis of local tissue cells, as well as the rupture of the cell membrane, resulting in leakage of serum ferritin from damaged cells. As a result, ferritin is significantly increased in the inflammatory response. However, there is still no report about the correlation of ferritin in MPP with hypoxia. Some studies on RMPP reported that when the ferritin level was 230 ng/mL or higher, the sensitivity and specificity for diagnosing refractory MP pneumonia were 67% and 67% respectively. In our study, the optimal cutoff point for ferritin was 411 ng/mL, with 86.4% sensitivity and specificity. The reason for the difference may be that the case we studied is RMPP itself, and the condition is more serious.

Systemic glucocorticoids can be considered for severe MPP with acute onset, rapid progression, especially for RMPP. However, there is no corresponding indicator for the use and timing of hormone dose. There are different opinions on the dosage of hormones in the existing literatures: You and Lee et al. used methylprednisolone 10mg/kg/day (intravenous infusion 2 ~ 3d and suspension reduction within 1 week) or gamma globulin 1g/kg/d (1 ~ 2 times) for a small percentage of patients who failed oral treatment. All patients showed significant improvement in clinical and radiological manifestations within a few days without associated side effects. Lee et al. gave prednisolone 1mg/kg/day orally to 15 children with RMPP, and reduced the dosage for 7d after continuous administration for 3-7d, which showed obvious effect in the treatment of children with RMPP. Luo et al. prospectively demonstrated that oral prednisone (2mg/kg/day) was more effective than azithromycin alone in children with RMPP. And Tamura gave 6 RMPP patients with methylprednisolone 30 mg/kg/day continuous intravenous drip in 3 d, the body temperature of all the patients returned to normal within 14 h, and their clinical symptoms improved significantly. They think that compared with conventional therapy, combined use of hormone treatment can reduce the length of stay and the incidence of the RMPP, and no hormone adverse reactions. The study implied that elder children are prone to more severe presentations, higher incidence of extra-pulmonary complications and more serious radiological findings. The study suggested that the severity of RMPP was related to host immune...
response, and the optimal values of CRP, LDH, FER and leukocyte classification neutrophils (CRP44.45mg/L, LDH590IU/L, FER411ng/L, leukocyte classification neutrophils 73.75%), lung consolidation, and pleural effusion may be the clinical characteristics of RMPP treated with pulse dose methylprednisolone.

This study indicated that in the treatment of refractory Mycoplasma pneumonia, timely use of appropriate doses of glucocorticoids can reduce the intensity of local inflammation, alleviates the immune reaction, and promote disease recovery. Therefore, under effective anti-infective therapy, glucocorticoid is effective, safe and convenient, and significantly speeds up the healing process proving itself a vital means for the treatment of refractory Mycoplasma pneumonia. During the treatment of RMPP with glucocorticoid, blood pressure, blood glucose, blood potassium and liver function should be monitored, and pay attention to the adverse reactions such as circulatory system and gastrointestinal bleeding, and pay attention to ECG monitoring during shock dose treatment. And pay attention to: the suitable time for treatment; exclude whether there are other infections or lesions; prevent the occurrence of double infection.

The study has some limitations. Firstly, it was a retrospective study, therefore there may have been some selection bias, so a large number of children with RMPP are need to be recruited and further prospective studies are needed to be carried out, however, considering that RMPP may be life-threatening, prospective study may have a harmful impact on children. Therefore, retrospective study may still be the way to study the issues. Secondly, the distribution of patients between the two groups is not matching, which may affect the statistical results. Thirdly, the patients come from the same region, the risk factors associated with glucocorticoid resistance may not be applicable to patients in other regions, requiring multicenter studies in the future. Fourth, our hospital is a tertiary hospital with many critically ill patients. The uneven distribution of critically ill patients in this study has a certain impact on the experimental results. Fifth, there may be some cases in which the patients had a combined MP and other pathogens infection which cannot be detected, which might result in RMPP. Finally, the optimal value of risk factor obtained by ROC curve may have some limitations and only guide judgment to a certain extent. More clinical data should be accumulated and further verified in clinical work for a more accurate reference standard.

Conclusion

Our research shows that excessive immune inflammatory response may play an important role in RMPP. CRP44.45mg/L, LDH590IU/L, FER411ng/L, leukocyte classification of neutrophils is 73.75%, lung consolidation, and pleural effusion may be clinical features that guide the treatment of RMPP children with pulse dose of methylprednisolone.

Abbreviation

MP: Mycoplasma Pneumoniae; CAP: Community Acquired Pneumonia; RMPP: Refractory mycoplasma pneumoniae pneumonia; PCR: Polymerase chain reaction; CRP: C-reactive protein; LDH: Lactate
Dehydrogenase; PCT: Procalcitonin; IL: Interleukin; La: lactic acid; Fer: Ferritin; D-D: D-dimer; Fg: Fibrinogen; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ROC: Receiver operating characteristic

Declarations

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Authors’ contributions

Conception and Design: ZLZ, TQZ, and YSX; Extraction of Data: ZLZ, WG, YYL, and JT; Drafting the Article: ZLZ; Revising It for Intellectual Content: ZLZ, and YSX; Final Approval of the Completed Article: ZLZ, TQZ, and YSX. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

All procedures performed in studies involving human participants were following the Ethics Committee of Tianjin Children's Hospital. This article does not contain any studies with animals performed by any of the authors. The data used in this study were anonymized before its use.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

Author details

1Tianjin Medical University, No.22, Qixiangtai Road, Heping District, Tianjin 300070, China.
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