

The clinical characteristics of *Mycoplasma pneumoniae* pneumonia and its relationship between hypokalemia in west China

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Background: *Mycoplasma pneumoniae* (MP) is one of the most common respiratory pathogens of community acquired pneumonia (CAP) in children. The purpose of this study was to identify epidemics of *Mycoplasma pneumoniae* pneumonia (MPP) and to determine the relationship between hypokalemia and MPP. **Methods:** This study was retrospectively conducted from 1 August 2016 to 31 July 2018 at Bishan People's Hospital in Chongqing, China. We analyzed the demographic characteristics (age, gender), extra-pulmonary manifestations, fever duration, length of hospital stay, whole blood cell (WBC) count, C-reactive protein (CRP) levels, and lactate dehydrogenase (LDH) levels.

Results: The total number of children with pneumonia was 3,385, including 570 (16.84%) patients in the MP infection group. The male-to-female ratio was 1.34:1. The peak time of MPP incidence was in autumn. The MP infection group had a significantly higher ratio of fever, higher body temperature, and longer fever duration. The number of MP-infected patients with hypokalemia was highest in spring. The length of hospital stay in the mild hypokalemia group was longer than in the normokalemia group. Furthermore, severe hypokalemia cases were all in the severe MP infection group, and the severity of MP infection and hypokalemia were positively correlated.

Conclusions: In this study, we concluded that children infected with MP were more susceptible to fever, and had a longer duration of fever. The number of MP-infected patients with mild hypokalemia peaked in spring, and affected more boys than girls. Furthermore, patients with severe hypokalemia had longer fever duration, and a correlation was found between the severity of MP infection and hypokalemia.

Keywords: Mycoplasma pneumoniae pneumonia (MPP); fever; hypokalemia

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Introduction

Mycoplasma pneumoniae (MP) is one of the most common respiratory pathogens of community acquired pneumonia (CAP), accounting for 20–40% of pneumonia in children (1,2). *Mycoplasma pneumoniae* pneumonia (MPP) contributes

to a broad array of pulmonary complications, such as pulmonary necrosis and chronic interstitial fibrosis (3), and has therefore attracted significant clinical attention. Recent evidence has shown that MP infection is also connected with the onset of several extra-pulmonary diseases, involving

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the skin, musculoskeletal, hematological digestive, nervous, and renal systems (4).

Potassium (K⁺), the most abundant cation in humans, which is essential for normal cellular function. It can prevent myocardial failure through weakening cellular hyperpolarity and depolarization (5,6). Hypokalemia is defined as a serum K⁺ level of less than 3.5 mmol/L, and hyperkalemia is defined as K⁺ levels above 5.5 mmol/L. A previous study reported that the degree of hypokalemia was associated with some clinical menifestations including high body temperature, and elevated laboratory indices reflecting myocardial injuries (7). Chen *et al.* (8) reported that patients with severe COVID-19 and severe hypokalemia (K⁺ levels below 3 mmol/L) experienced respiratory muscle dysfunction and ventricular arrhythmia , both of which can be life-threatening.

There were no reports about the relationship between hypokalemia and MPP. We conducted this study to identify epidemics of MPP in west China, and to explore the relationship between hypokalemia and MPP.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi. org/10.21037/tp-20-471).

Methods

Study population

This study was retrospectively conducted at the Bishan People's Hospital in Chongqing, China. Patients included hospitalized children with MPP, without vomiting or diarrhea. Data from patients were analyzed anonymously between 1 August 2016 and 31 July 2018.

Definitions

MPP was diagnosed according to the following criteria: (I) clinical presentation (fever, cough), (II) chest imaging with pulmonary infiltrates, (III) positive results for MP with serum anti-MP IgM titer \geq 1:160.

Children with any of the following factors were excluded: (I) neonatal pneumonia, (II) diarrhea, which was defined as the passage of 3 or more abnormally loose or watery stools in the previous 24 hours (9), (III) convalescent pneumonia, (IV) long-term use of glucocorticoids or immunosuppressive agents, and (V) congenital heart or chronic lung disease.

Ethics statement

The study was conducted in accordance with the guiding principles of the Declaration of Helsinki (as revised in 2013), and the study approach was approved by the Ethical Review Committee of Bishan People's Hospital. This study only collected the clinical data of patients, did not interfere with the treatment plan of patients, and did not bring physiological risks to patients. Because of the retrospective nature of the study, patient consent for inclusion was waived. We did our best to protect the privacy of personal information provided by patients.

Clinical data

Medical records of the study population were retrospectively reviewed. We collected the records including demographic characteristics (age, gender), extra-pulmonary manifestations, fever duration, and length of hospital stay from all children included in the study. The data were registered by our own pediatricians. We finally used months as a unit of age.

Laboratory data

Peripheral blood samples were obtained on admission for the determination of WBC, CRP, LDH, and specific antibody to MP. All the examinations were completed in accordance with the standard protocol of the laboratory department. The report results were reviewed by 2 different medical lab staff members and released to the patients.

Statistical analysis

Continuous variables were presented as medians with 25% and 75% quartiles (interquartile range, IQR), and the non-parametric test and Mann-Whitney U test were used for analysis. Categorical variables were presented as counts (percentages), and assessed using the Kruskal-Wallis test or Fisher's exact test. Correlations between variables were analyzed using Pearson's correlation coefficient. Binary logistic regression tests were used to evaluate the association between the severity of MP infection and potassium. Statistical analyses were conducted using SPSS 25.0.

Table 1 Characteristics of children with pneumonia from 1 August 2016 to 31 July 2018

Item	No MP infection	MP infection	Р
Cases, n (%)	2,815 (83.16)	570 (16.84)	
Sex (male), n (%)	1,622 (57.60)	318 (57.80)	0.420
Age (months), median [IQR]	24 [10–49] 22 [9–46]		0.143
Season at enrollment, n (%)			0.002
Spring (March–May)	751 (26.70)	148 (26.00)	
Summer (June–August)	575 (20.40)	83 (14.60)	
Autumn (September–November)	731 (26.00)	181 (31.80)	
Winter (December-February)	758 (26.90)	158 (27.70)	
Heart rate [bpm], median	121 [115–127]	116 [109–122]	0.000
Respiratory rate [bpm], median	32 [28–37]	28 [25–32]	0.000
Fever, n (%)	1,743 (61.90)	398 (69.80)	0.000
Max temperature (°C), median	39 (38.5–39.5)	39.2 (38.7–39.5)	0.001
Fever duration [day], median	4 [2–5]	4 [2–6]	0.000
Wheezing, n (%)	585 (20.80)	92 (16.10)	0.012
Length of stay [day], median	5 [4–6]	5 [4–6]	0.599
WBC count (×10 ⁹ /L), median (IQR)	9.83 (7.32–13.80)	9.26 (6.96–12.19)	0.017
Ratio of neutrophils (%), median (IQR)	47 (32.60–61.60)	57.7 (44.30–67.90)	0.000
CRP (mg/L), median (IQR)	2.64 (0–9.71)	3.74 (0–9.97)	0.303
LDH (U/L), median [IQR]	281 [245–322]	261 [227–294]	0.000

MP, Mycoplasma pneumoniae; IQR, interquartile range; WBC, whole blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Results

Characteristics of children with pneumonia

As shown in *Table 1*, the total number of children with pneumonia was 3,385, including the no MP infection group with 2,815 (83.16%) patients and the MP infection group with 570 (16.84%) patients. Age ranged from 1 month to 178 months, with a mean age of 32.7 ± 29.88 months. The male-to-female ratio was 1.34:1. Cases were found more frequently during spring, autumn, and winter: from March to May in 899 cases (26.6%), from June to August in 658 cases (19.4%), from September to November in 912 cases (26.9%), and from December to February in 916 cases (27.1%).

Age and gender distribution

The median age of the MP infection group (22 months,

IQR, 9–46 months) was similar to that of the no MP infection group (24 months, IQR, 10–49 months, P=0.143). There were 1,622 boys in the no MP infection group (57.6%) and 318 boys in the MP infection group (57.8%, P=0.143).

Seasonal distribution

The no MP infection group and the MP infection group had 751 cases (26.7%) and 148 cases (26.0%) in spring, 575 cases (20.4%) and 83 cases (14.6%) in summer, 731 cases (26.0%) and 181 cases (31.8%) in autumn, and 758 cases (26.9%) and 158 cases (27.7%) in winter, respectively (P=0.000). The number of cases between the groups was significantly different, especially in summer and autumn (P=0.000). In addition, we found that the peak time of MPP incidence was in autumn.

Clinical symptoms

The clinical characteristics of the no MP infection group and the MP infection group are shown in *Table 1*. Among the children with MP, the most common respiratory symptoms were fever and wheeze, prompting us to compare the clinical conditions of the 2 groups.

The MP infection group had a significantly higher ratio of fever (398/570, 69.8%) than that of the no MP infection group (1,743/2,815, 61.9%, P=0.000). Furthermore, the MP infection group had higher body temperature (median 39.2 °C, IQR, 38.7–39.5 °C, P=0.001) and longer fever duration (median 4 days, IQR, 4–6 days, P=0.000).

Our study also showed that the MP infection group had a significantly lower ratio of wheeze (92/570, 16.1%) than that of the no MP infection group (585/2,815, 20.8%, P=0.012). In addition, the MP infection group had a lower heart rate (116 vs. 121 bpm, P=0.000) and a lower respiratory rate (28 vs. 32 bpm, P=0.000) compared to the no MP infection group.

Laboratory tests

The whole blood cell (WBC) count of the MP infection group (median 9.26×10^{9} /L, IQR, $6.96-12.19 \times 10^{9}$ /L) was lower than that of the no MP infection group (median 9.83×10^{9} /L, IQR, $7.32-13.80 \times 10^{9}$ /L, P=0.017). However, the ratio of neutrophils was higher in the MP infection group than in the no MP infection group (P=0.000). CRP was higher in the MP infection group (median 3.74 mg/L, IQR, 0–9.97 mg/L) than in the no MP infection group (median 2.64 mg/L, IQR, 0–9.71 mg/L) (P=0.303), while both groups were within the normal reference range.

MPP and potassium

In order to study the effect of potassium on MP, especially the effect of hypokalemia, we divided the patients with confirmed MPP into 4 groups: normokalemia group, mild hypokalemia group, severe hypokalemia group, and hyperkalemia group. The specific data are presented in *Table 2*. Out of the 570 patients with MP in this study, the 4 groups had 489, 73, 4, and 4 patients, respectively.

We found that there were no female patients with hypokalemia, but there were 73 male patients with mild hypokalemia and 4 male patients with severe hypokalemia (P=0.000). There were 148, 83, 181, and 158 patients with MP infections across the 4 seasons, respectively. In order to determine whether season had an effect on potassium, we found that there were 105 cases (21.5%) and 41 cases (56.2%) in spring, 70 cases (14.30%) and 13 cases (17.8%) in summer, 177 cases (36.2%) and 1 case (1.4%) in autumn, and 137 cases (28%) and 18 cases (24.7%) in the normokalemia group and the mild hypokalemia group, respectively. The differences between groups across the seasons were statistically significant (P=0.000). Furthermore, there were more normokalemia cases in autumn (36.2%), but more cases with mild hypokalemia in spring (56.2%), and the difference between the normokalemia group and the mild hypokalemia group was statistically significant (P=0.000). All these data demonstrated that the number of patients with MP infection and hypokalemia was higher in spring. After analyzing the age distribution, we found that the age of the mild hypokalemia group (median 17 months, IQR, 2.75-20 months) was lower than that of the normokalemia group (median 25 months, IQR, 10-47 months, P=0.007). This finding indicated that patients with mild hypokalemia were younger than patients in the normokalemia group.

The length of hospital stay in the mild hypokalemia group (median 6 days, IQR, 6–7 days) was longer than that of the normokalemia group (median 5 days, IQR, 4–5 days, P=0.000).

There were no differences in the ratio of fever, maximum temperature, and the duration of fever among the 4 groups. However, among the fever cases, the severe hypokalemia group had a longer fever duration (median 8 days) compared to the normokalemia group (median 4 days, IQR, 2-6, P=0.037) and the mild hypokalemia group (median 4 days, IQR, 3-5.5 days, P=0.035). The results demonstrated that patients with severe hypokalemia had a longer fever duration.

Results also demonstrated that there were no marked differences in WBC, ratio of neutrophils, CRP, and LDH among the 4 groups.

In order to determine the relationship between hypokalemia and the titer of serum anti-MP IgM, we found that across the 4 groups, there were 477 cases (86.3%), 72 cases (13%), 0 cases (0%), and 4 cases (0.7%) in the mild MP infection group, respectively, and 412 cases (70.6%), 1 case (1.4%), 4 cases (23.5%), and 0 cases (0%) in the severe MP infection group, respectively. The differences were statistically significant (P=0.000). Furthermore, the severe hypokalemia patients were all in the severe MP infection group, and logistic regression analysis also showed that the severity of MP infection and potassium levels were

Table 2 The characteristics of MPP with hyperkalemia and different levels of hypo	kalemia
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Item	Normokalemia group	Mild hypokalemia group	Severe hypokalemia group	Hyperkalemia group	Ρ
Case, n	489	73	4	4	
Gender					
Male, n	238	73	4	3	0.000
Female, n	251	0	0	1	
Age (months), median [IQR]	25 [10–47]	17 [7–35]	9.5 [2.75–20]	1 [1–10]	0.007
Season at enrollment, n (%)					0.000
Spring (March–May)	105 (21.5)	41 (56.2) [@]	2 (50.0)	0	
Summer (June–August)	70 (14.3)	13 (17.8)	0	0	
Autumn (September–November)	177 (36.2)	1 (1.4) [@]	1 (25.0)	2 (50.0)	
Winter (December-February)	137 (28.0)	18 (24.7)	1 (25.0)	2 (50.0)	
Heart rate (bpm), median [IQR]	116 [109–122]	117 [108–121]	109 [98–117]	109 [98–123]	0.471
Respiratory rate [bpm], median	28 [25–32]	28 [25–32]	29 [24–33]	28 [22–34]	0.972
Fever, n (%)	339	54	3	2	0.694
Max temperature (°C), median	39.2 (38.7–39.5)	39 (38.4–39.5)	38.5	39.3	
Fever duration [day], median	4 [2–6]	4 [3–5.5]	8#	5.5	
Wheezing, n (%)	81	9	1	1	0.726
Length of stay (day), median	5	6	6	3.5	0.000
WBC count (×10 ⁹ /L), median (IQR)	9.32 (6.98–12.46)	8.60 (6.82–11.34)	8.97 (4.90–12.45)	8.86 (6.01–17.96)	0.818
Ratio of neutrophils (%), median (IQR)	57.10 (44.05–67.60)	61.35 (44.95–70.33)	57.75 (48.83–58.58)	59.60 (29.25–73.98)	0.996
CRP (mg/L), median (IQR)	9 (0–9.51)	4.56 (0–11.49)	2.71 (0–10.45)	2.91 (0–6.80)	0.700
LDH (U/L), median	261.5 (225.0–295.0)	261 (228.5–289.0)	241	311.5 (213.8–364.2)	0.753
Mild MP infection (serum anti-MP IgM titer =1:160), n (%)	477 (86.3)	72 (3.0)	0 (0.0)	4 (0.7)	
Severe MP infection (serum anti-MP IgM titer ≥1:320), n (%)	12 (70.6)	1 (1.4)	4 (23.5)	0 (0.0)	

^e, mild hypokalemia group *vs.* normokalemia group, P<0.05; [#], severe hypokalemia group *vs.* normokalemia group, P<0.05; [%], severe hypokalemia group *vs.* mild hypokalemia group, P<0.05. MP, *Mycoplasma pneumoniae* pneumonia; IQR, interquartile range; WBC, whole blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase.

correlated (r=0.98, P=0.002).

Discussion

In our study, the incidence of MP was 16.84% and the male-to-female ratio was 1.34:1, which was generally consistent with the reported data (10). Seasonal forcing has been proposed as a determinant for the periodic patterns in some infectious diseases. Our results suggested that MPP

occurred all year round, but the incidence was lowest in summer and highest in autumn. This is different from some previous reports, including a study by Waites *et al.* (11) who found that MP infections tended to be more common in summer or early autumn. Previous results have also shown that elements of the local climate such as higher temperature and relative humidity can influence MPP incidence (12-14). Hence, the distributions of MP may vary across the year, and this may be different among different cities and countries.

Notably, our study revealed that the pattern of positive detections stratified by age. With detection in all age groups, there was no difference among groups in our study. This is in contrast to a previous report showing that MP cases were classically observed among pre-school or schoolaged children (11,15). However, another study showed that 39.2% of children aged from 0-4 years were diagnosed with MMP infection (12). IgM antibodies are used for the diagnosis of MP infection, though elevated IgM will decay slowly up to 6 months. Thus, doctors are not sure whether the reaction is from current infection or from a primary abnormality. In our study, we also used IgM antibodies for the diagnosis of MP infection, but the median age of the MP infection group was 22 months (IQR, 9-46 months), which was school age. Hence, we believed the IgM test was the most efficient way to make a serological diagnosis in a single laboratory examination compared to other diagnostic tests.

Among children with MP infection, the most common respiratory symptoms were cough, dyspnea, fever, and wheeze. Fever is a common clinical symptom in children and is one of the leading causes for medical consultation and hospital admissions (16). In our study, we found that the patients with MP infection (51.5%) had a higher ratio of fever than those with no MP infection (11.7%, P=0.000). At the same time, patients with MP infection also had a longer duration of fever. We inferred that patients with MP infection were more susceptible to fever. Therefore, even MP is a self-limited disease, and can cause a higher ratio of fever and a longer duration of fever, making these children less comfortable, warranting more attention to this problem. Reports have suggested that MP plays a role in acute episodes of wheezing, and is also associated with the development of asthma (14,17). However, in our study, patients with MP infection (2.7%) had a lower ratio of wheeze than those with no MP infection (17.3%, P=0.011). The median age of the MP infection group and the no MP infection group were 22 and 24 months, respectively, which was in early childhood. It is known that viruses are the main cause of wheeze during this period (2).

As many as 25% of people infected with MP may experience extra-pulmonary complications (18), and MPrelated extra-pulmonary diseases represent the most evident clinical problem of this infection, especially in children (19). MP can adhere to other cells, such as red blood cells and macrophages (14). In our study, we found that the WBC count was lower in the MP infection group than

in the no MP infection group (P=0.034), but the ratio of neutrophils and CRP was higher in the MP infection group compared to the no MP infection group (P=0.000, P=0.312). This result was in agreement with previous data, which showed that the WBC count was mostly normal or slightly elevated, and neutrophils were found by the differential counts in the cases of MP infection. Stevens and Krause (20) also observed that 64% of cases had normal WBC count. Furthermore, Gao et al. (21) showed that children with positive MP serology had higher CRP levels. Therefore, in our clinical work, if routine blood examination shows that the WBC count is at a normal or slightly elevated level and the ratio of neutrophils and CRP is higher, we can conclude that the patient may have MP infection. LDH is released from cells after cell damage, and the LDH level can reflect the degree of cell and tissue damage. In this study, the levels of LDH were higher in the no MP infection group than in the MP infection group, but all were within the normal range. A higher level of LDH can translate into excessive inflammatory cell infiltration and severe lung injury, which is indicative of refractory MPP (RMPP). Therefore, serum LDH level has been considered a marker for RMPP (22). However, in our study, there were few cases of RMPP, suggesting that for cases with no RMPP, LDH may have little clinical significance.

Hyponatremia, hypokalemia, and hypocalcemia have been reported in sick children. Hypokalemia gives rise to cellular hyperpolarity, increases resting potential, and hastens depolarization in cardiac cells and lung cells. Severe hypokalemia can result in ventricular arrhythmia and respiratory muscle dysfunction, which are life-threatening conditions in patients (8,23). More research and education about dyskalemia may help increase awareness about the issue and improve clinical practice. Our study found that patients with MP infection and hypokalemia were all males, and there was a strong association between gender and hypokalemia in MP-infected patients. In addition, patients with MP infection and hypokalemia had a longer length of hospital stay and the patients with severe hypokalemia had a longer duration of fever. This finding has never been reported, but we regret for the limit of the small sample scale. We also found that the cases of severe hypokalemia were all in the severe MP infection group, and logistic regression analysis showed that the severity of MP infection and potassium were negatively correlated. Therefore, patients with a higher titer of serum anti-MP IgM were more likely to be hypokalemic. We advise that children

with pneumonia who also have hypokalemia should receive closer observation at health care facilities in clinical practice. Hypokalemia is common in sick and hospitalized patients, but the severity can vary (23). Potassium content and its distribution rely on a complex interplay of multiple factors, including renal and gastrointestinal function, and diet (5). Findings have also shown a strong association between diarrhea and hypokalemia, as there may be a further reduction in potassium levels due to loss though diarrheal stools (24). However, in our study, we excluded patients with diarrhea and chronic diseases to eliminate interference.

Hyperkalemia (>5.5 mmol/L) has been associated with an increased risk of death, even when potassium levels reached 6.0 mmol/L (5). In this study, there were few patients with hyperkalemia, which might have impacted the level of statistical significance for some of the variables among groups. Based on these results, we propose that there may be some association between these factors, but further study is needed.

MP is one of the most common respiratory pathogens of CAP in children, it is of great significance to study it in depth. What our group can do is to last the study time and increase the sample size to find more interesting phenomenon.

In summary, our results indicated that children with MP infection were more susceptible to fever and had a longer fever duration, while patients with severe hypokalemia also had a longer duration of fever. We also found that the number of MP-infected patients with mild hypokalemia peaked in spring, affecting more boys than girls. Furthermore, a positive correlation was found between the severity of MP infection and hypokalemia.

Limitations

This study has a few limitations. Firstly, our study was performed prospectively using IgM antibodies for the diagnosis of MP infection. Methodologies for the detection of MP include nucleic acid amplification tests (NAAT), serology, and culture. But there are no internationally defined guidelines on MP (25). There are some limitations of the IgM test, but compared to other diagnostic tests, serological diagnosis is the most efficient in a single laboratory examination. Secondly, the severity of MP infection has there are several risk factors. The confounding factors might affect the results. However, as the present findings reflect the fundamental pathophysiological mechanisms of MP infection and the large proportion of patients with hypokalemia, we believe that our conclusions are valid. Lastly, the small sample size is the main limitation of our study, especially when the patients were grouped by potassium concentration. In future studies, more data using a larger sample size should be collected.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013), and the study protocol was approved by the Ethical Review Committee of Bishan People's Hospital. This study only collected the clinical data of patients, did not interfere with the treatment plan of patients, and did not bring physiological risks to patients. Because of the retrospective nature of the study, patient consent for inclusion was waived. We did our best to protect the privacy of personal information provided by patients.

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