

Clinical Analysis of Children with Mixed Macrolide-Resistant *Mycoplasma pneumoniae* Infection

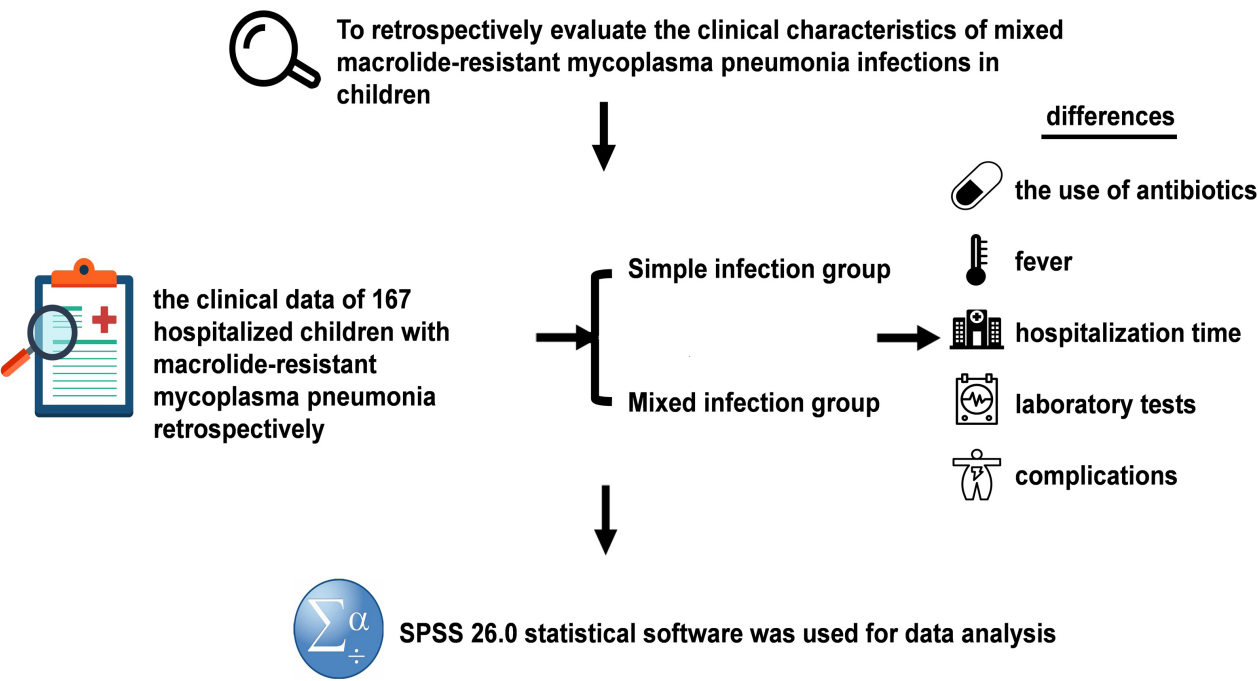
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Graphical Abstract



Clinical Analysis of Children with Mixed Macrolide-Resistant *Mycoplasma pneumoniae* Infection

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Abstract

Purpose: Epidemiological data from Asia have documented the rapid and widespread emergence of macrolide resistance in *Mycoplasma pneumoniae* (MP). This paper aims to retrospectively evaluate the clinical characteristics of mixed macrolide-resistant *Mycoplasma pneumoniae* (MRMP) infections in children.

Methods: The study included 167 hospitalized children with MRMP. We analyzed the children's clinical data retrospectively, and compared the differences in the use of antibiotics, fever, hospitalization time, laboratory tests and complications between the mixed infection group and the separately infected group before admission.

Results: Compared with the separately infected group, hospitalized children with mixed infection had a longer hospital stay, and there was a significant difference between the two ($P < 0.05$); Alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), and platelet count (PLT) of children in the mixed infection group were significantly higher than those in the separately infected group ($P < 0.05$); and the incidence of hepatic function impairment, cardiac enzyme profile abnormality, and pleural effusion in the children in the mixed infection group was higher than that in the separately infected group ($P < 0.01$).

Conclusion: Patients with MRMP combined with mixed infections had prolonged hospital stays, increased systemic inflammatory response, and increased incidence of extrapulmonary complications compared with those with simple infections.

Keywords: *Mycoplasma pneumoniae*; Macrolide resistance; Mixed infection; Hospitalized children

Introduction

MP is one of the major pathogens causing community-acquired pneumonia (CAP) in children and adolescents, accounting for up to about 40% of cases [1]. While pneumonia caused by MP is typically a self-limiting disease [2], some patients may develop refractory *Mycoplasma pneumoniae* pneumonia (RMPP) [3] or extrapulmonary complications [4,5]. Macrolides are currently the first-line agents for treating *Mycoplasma pneumoniae* pneumonia (MPP) in pediatric populations. However, the widespread use of macrolides has resulted in a sustained increase in antibiotic resistance prevalence, with significant regional variations. Mutations at nucleotide sites A2063, A2064, A2067, and C2617 within the 23S rRNA domain V of MP are recognized as markers of MRMP [6]. Among these, the A2063G mutation is the most frequently identified in resistant isolates [7]. Mixed infections have been reported to be more common in children with MPP, in which disease severity is higher than in single pathogen infections [8,9]. Relevant studies have shown that co-infection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with MP during the Coronavirus Disease 2019 (COVID-19) pandemic may lead to prolonged Intensive Care Unit (ICU) hospitalization or exacerbation of clinical symptoms

in patients [10,11].

In this study, we analyzed the clinical characteristics and laboratory test results of children with MRMP and mixed infections in Hefei, aiming to identify children with MRMP with mixed infections at an early stage, and to guide clinicians to intervene in the rational use of antibiotics and therapeutic measures as a means of reducing complications, shortening the hospitalization time of the children, and improving the prognosis.

Methods

Study Design and Population

The clinical data of 167 children diagnosed with MPP in the First Affiliated Hospital of Anhui Medical University were collected. All children were diagnosed with MPP according to WHO's CAP clinical diagnostic criteria [12], including symptoms and chest X-rays assessed by clinicians. Inclusion criteria: (1) age from 5 months to 15 years; (2) positive MP PCR or positive serologic tests; (3) macrolide antibiotic resistance; (4) complete clinical data. Exclusion criteria: (1) immunocompromised; (2) chronic lung disease (except asthma), chronic heart disease; (3) diseases of the blood

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system; (4) incomplete clinical data.

Data Collection and Variables

The clinical data of the children were collected, including gender, age, previous antibiotic use during the disease and clinical symptoms such as fever, cough, sputum, rash, and duration of symptoms before hospitalization. In addition white blood cell count (WBC), percentage of neutrophils (NEU), percentage of monocytes (MON), PLT, fibrinogen (FIB), thrombin time (TT), D-dimer (DD), fibrinogen degradation product (FDP), CK, urea (UREA), blood creatinine (CRE), uric acid (UA), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), procalcitonin (PCT), activated partial thromboplastin time (APTT), prothrombin time (PT), ALT, AST, LDH, and total protein (TP), chest X-ray, and complications: Hepatic impairment, pleural effusion, ketonuria, pulmonary atelectasis, coagulation disorders, micronutrient deficiencies and abnormalities in cardiac enzyme profiles.

Detection of MP drug resistance genes

The presence of mutations at the A2063 and A2064 loci was determined by pyrophosphate sequencing of the two portions of the 23S rRNA gene structural domain V. The extracted nucleic acids were reverse transcribed into the nucleic acids of the A2063 and A2064 loci. The extracted nucleic acids were reverse transcribed into cDNA for amplification (11121ES, Yeason Biotech Co., Shanghai, China). Positions 2063 and 2064 in the structural domain of the 23SrRNA gene were amplified using PCR as described below. PCR system: ddH₂O 16 µl, 2×Taq Master Mix 25 µl, Forward primer1 (10 µM) 2 µl, Reverse primer2 (10 µM) 2 µl. cDNA 5µl, the total system was 50µl. program: 95°C 3min; 95°C 15S, 60°C 15S, 72°C 60S cycle 35 times; 72°C 5min. the PCR products were compared with the MP standard gene (23SrRNA gene, GenBank no. X 68422) after bidirectional sequencing by Anhui General Biological Company [13].

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. According to data types, categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as medians and quartiles. Normal distribution was expressed as mean ± standard deviation, and non-normal distribution was expressed as interquartile spacing. When comparisons were made between two groups, normal distribution was tested by the t test; non-normal tests were tested by the rank sum test. Count data were compared using χ^2 or corrected χ^2 . $p < 0.05$ was considered statistically significant.

Ethics Approval

The current investigation was duly approved by the human ethics council of Anhui Medical University's First Affiliated Hospital (Approval No: Quick-PJ 2023-08-41). The written informed consent was obtained from patients in accordance with the Declaration of Helsinki.

Results

Study of drug-resistant gene mutations of MP

In this study, 167 MP nucleic acid positive patients were amplified and sequenced at the above loci. The results showed that the A2063G mutation in the V region of the 23SrRNA gene was found in all 167 (167/167,100%) patients, and no drug-resistant mutation was found in the A2064G/A2064C locus.

Comparison of clinical symptoms on admission between the two groups

According to the results in Table 1, most of the patients were on antibiotics before admission. The length of hospitalization in the mixed infection group was significantly longer than that in the simple infection group, and the difference between the two groups was statistically significant ($Z = -6.607$, $p < 0.001$); however, the clinical symptoms exhibited by the patients, such as fever, cough, sputum, vomiting, rash, and dizziness, were not statistically significant between the two groups.

Table 1 Comparison between clinical symptoms in simple and mixed infection groups

	Simple infection group (n=117)	Mixed infection group (n=50)	$\chi^2/t/Z$ value	p value
Use of antibiotics before admission	116(99.1)	49(98.0)	0.000 [#]	>0.999
Length of hospitalization (d)	4.0(4.0,6.0)	7.0(5.8,8.0)	-6.607	<0.001
ICU	14(11.9)	10(20.0)	1.837	0.175
Fever	114(97.4)	48(96.0)	0.249	0.618
Cough	114(97.4)	47(94.0)	1.194	0.275
phlegm	72(61.5)	24(48.0)	2.627	0.105
Vomiting	14(28.0)	10(20.0)	1.837	0.175
Rash	4(3.4)	0(0)	0.594 [#]	0.441
Dizziness	2(1.7)	0(0)	0.024 [#]	0.878

[#]chi-square test continuity correction

Comparison of relevant laboratory test indexes between the two groups

The PLT, ALT, AST, LDH and CK of the children in the mixed infection group were elevated and higher than those in the simple infection group, and the difference was statistically significant ($P < 0.05$), especially for ALT and LDH ($P < 0.001$). While other blood routine related indexes, coagulation function indexes and renal function indexes were compared, the

difference was not statistically significant ($P > 0.05$). See Table 2.

Comparison of complications between the two groups

The incidence of complications of pleural effusion, liver function impairment and cardiac enzyme spectrum abnormality was higher in the mixed infection group than in the simple infection group, and the difference was statistically significant ($P < 0.05$). There was no significant difference in the incidence of coagulation dysfunction, ketonuria, pulmonary atelectasis and micronutrient deficiency between the two

groups ($P > 0.05$).

Discussion

MP is microorganisms intermediate between cells and viruses that cause respiratory infections [14] and is one of the major pathogens causing community-acquired pneumonia in children, prevalent in children aged 4-6 years [15]. MP infections exhibit a range of signs and symptoms from asymptomatic infections to severe and potentially fatal

Table 2 Comparison of laboratory test results between simple infection group and mixed infection group

	Simple infection group	Mixed infection group	t/Z value	P value
WBC	6.66(5.61,8.89)	7.12(5.82,9.23)	-1.213	0.225
NEU	59.98±12.46	61.04±13.70	-0.490	0.624
LYM	31.00±12.05	30.68±13.34	0.150	0.881
MON	6.50(5.35,8.30)	5.95(4.78,7.75)	-1.384	0.166
PLT	301.00(251.00,362.50)	344.00(266.00,414.25)	-1.966	0.049
CRP	9.24(3.11,20.56)	10.33(2.21,20.21)	-0.687	0.492
PCT	0.08(0.05,0.10)	0.08(0.05,0.14)	-0.055	0.956
PT	12.60(12.10,13.00)	12.58(12.10,13.00)	-0.005	0.996
APTT	38.78±5.76	38.91±4.73	-0.160	0.873
FIB	4.59(4.06,5.04)	4.50(3.94,5.03)	-0.650	0.516
TT	16.80(16.20,17.20)	16.57(16.05,17.20)	-1.269	0.204
DD	0.68(0.42,1.06)	0.55(0.36,0.89)	-1.595	0.111
FDP	2.71(2.05,3.86)	2.33(1.52,3.69)	-1.319	0.187
TP	68.4(64.9,72.7)	67.4(64.1,72.18)	-0.606	0.544
ALT	16.00(13.00,20.00)	23.00(15.00,33.25)	-4.073	<0.001
AST	29.00(24.50,34.00)	31.50(25.00,49.25)	-2.223	0.026
LDH	289.00(259.00,346.00)	342.50(304.25,450.25)	-4.108	<0.001
CK	71.00(45.5,106.00)	92.00(60.25,230.20)	-2.473	0.013
UREA	3.19(2.47,3.83)	3.23(2.64,3.89)	-1.148	0.251
CRE	32.60±7.79	31.03±7.61	1.198	0.860
UA	221.00(185.50,289.00)	214.5(185.00,260.00)	-0.620	0.535
eGFR	185.00(178.00,209.00)	195.00(179.25,223.50)	-0.699	0.485

Table 3 Comparison of complications between the simple infection group and the mixed infection group (cases (x/%))

	Simple infection group	Mixed infection group	$\chi^2/t/Z$ value	P value
Pleural effusion	5(4.3)	13(26.0)	17.195	<0.001
Lung atelectasis	17(14.5)	9(18.0)	0.321	0.571
Hepatic impairment	5(4.3)	10(20.0)	10.597	0.001
Ketonuria	7(6.0)	7(14.0)	1.981	0.159
Coagulation abnormalities	36(30.8)	10(20.0)	2.124	0.145
Abnormal cardiac enzyme profile	1(0.8)	7(14.0)	13.727	<0.001
Micronutrient deficiencies	44(37.6)	17(34.0)	0.197	0.658

intra- and extra-pulmonary complications.

It has been documented that the co-infection rate of MP with other respiratory infection pathogens is 88.49% [16]. However, in some cases, these co-infections can lead to severe disease. In this study, when MRMP was co-infected with other pathogens, the length of hospitalization was prolonged, and in addition, the serum levels of ALT, AST, LDH, and CK were increased in patients, which may be related to the extrapulmonary complications of MP infection and the activation of the immune response in children's organisms [17]. In recent years for the treatment of MPP in children the first choice is macrolides, which to some extent can relieve the symptoms of patients. However, overuse of macrolides has resulted in the development of macrolide-resistant antibiotic resistance. Since the first isolation of drug-resistant strains from patients in Japan in 2001, countries have begun to emphasize and monitor the occurrence of resistance rates. In China, there is some variability in the resistance rate in each region. For example, the resistance rate was 60.33% in Guangyuan [18] and 93.88% in Yunnan [19]. The results of this study found that the resistance mutation rate in Hefei region during the MP epidemic was as high as 100% and was a mutation at the A2063G locus, which is the mutation locus with the highest incidence in China at present [20].

Research has found that during follow-up of some pediatric patients treated with azithromycin according to standard protocols, some patients developed antibiotic-resistant gene mutations within 2 to 4 weeks [18], indicating that antibiotics can induce resistant mutations or select for resistant strains in the short term. This highlights the importance of avoiding unnecessary antibiotic use. Additionally, studies have shown that macrolide antibiotics have some efficacy against MRMP infections, but this is not because MRMP is sensitive to macrolide antibiotics, but rather due to the self-limiting nature of MP infections and the anti-inflammatory effects of macrolide drugs [21]. Other studies have also found that the use of macrolide antibiotics does not provide significant benefits for mild MP infections [22]. Therefore,

the standardized use of macrolide drugs is essential. It is crucial to continue strictly adhering to the standards for the use of macrolide antibiotics to reduce the emergence and spread of drug-resistant strains. Clinicians should promptly monitor the drug resistance of MRMP patients and rationally select antimicrobial drugs to minimize the emergence of drug-resistant strains, thereby providing a scientific basis for MP treatment. Avoiding unnecessary antibiotic use and curbing the emergence of microbial drug resistance is of critical importance to children, families, and the healthcare system. Children with MPP primarily present with fever and cough. Early pulmonary signs may not be prominent, but as the condition progresses, decreased breath sounds, dry rales, and wet rales may appear. Severe Mycoplasma pneumoniae pneumonia (SMPP) typically occurs around one week into the illness, often accompanied by pulmonary and extrapulmonary complications. A small number of MPP cases may progress to critical illness, often presenting with prominent symptoms of dyspnea and respiratory failure. The Guidelines for the Diagnosis and Treatment of Mycoplasma Pneumonia in Children (2023 Edition) emphasize that the key to managing mycoplasma pneumonia lies in the early identification and treatment of SMPP and fulminant Mycoplasma pneumoniae pneumonia (FMPP). The optimal treatment window is within 5–10 days after the onset of fever. Early diagnosis and intervention for children with MP are crucial in preventing the occurrence of complications.

This study indicates that the incidence of liver function impairment and complications is higher in the mixed infection group than in the single infection group. Previous studies have shown that there are differences in LDH elevation between the resistant group and the sensitive group, while CRP changes are similar [23]. This not only confirms that MRMP exhibits a stronger immune response but also suggests that LDH is a more sensitive immunological indicator than CRP. Imaging findings are one of the primary bases for clinically assessing the severity of MPP in children and evaluating prognosis. Early imaging examinations aid in the early identification and

treatment of SMPP and FMPP, enabling the development of individualized treatment plans based on classification. For mild cases, systemic corticosteroids should not be routinely used in addition to anti-MP therapy. However, corticosteroids are frequently used in cases of MP infection complicated by excessive inflammatory responses. Studies have shown that corticosteroids can rapidly improve clinical and imaging findings in severe MPP [24]. The Chinese Expert Consensus on the Diagnosis and Treatment of MPP in Children also states that systemic corticosteroids may be considered for acute-onset, rapidly progressing, and severe MPP [25].

Domestic studies have found that among MP-associated viral infections, respiratory syncytial virus accounts for the highest proportion. While among MP-associated bacterial infections, *Streptococcus pneumoniae* and *Klebsiella pneumoniae* are more common [26]. Children with Epstein-Barr virus (EBV)-associated MP infections experience longer fever durations and are more prone to respiratory distress or pleural effusion, suggesting that during clinical treatment, when prolonged fever, respiratory distress, or pleural effusion occurs, the possibility of co-infection should be considered [27]. In the Taipei study, 64.7% of patients requiring ICU admission presented with pleural effusion, indicating a high incidence of pleural effusion as a comorbidity [28], which is similar to our results. WBC, PLT, Hb levels, fever duration, dyspnea, and pleural effusion are useful in diagnosing MPP in children with EBV infection. Multi-organ damage is exacerbated by mixed infections, which may involve complex immune response mechanisms. Some scholars have suggested that most extrapulmonary manifestations may be caused by disturbances in the adaptive immune response. Cellular and humoral immunity, including tissue-specific T cells and autoantibodies, may be involved in the pathogenesis of extrapulmonary manifestations of MP [29]. The results of this study showed that the occurrence of liver damage and cardiac enzyme profile abnormalities and pleural effusion was significantly higher in the mixed infection group than in the simple infection group in Hefei area. Therefore, the possibility of mixed infections is alerted to the occurrence of some complications in combination with the occurrence of some comorbidities in the children attending the clinic in Hefei area.

Our study has several limitations, first, the sample size was too small and from a single center, and also the condition of the children admitted to the hospital during the *Mycoplasma pneumoniae* outbreak may have been inherently more severe. These two points suggest some bias in our results. We acknowledge that our study may be subject to the inherent limitations of retrospective data collection and have taken steps to mitigate their impact. Selection bias was addressed by applying strict inclusion and exclusion criteria during participant/study selection. While retrospective designs have inherent limitations, we believe our rigorous methodology provides meaningful clinical insights.

Conclusion

In summary, this study found that during the outbreak of MP, the drug-resistant mutation rate of hospitalized children in Hefei was 100%, and that mixed infection of MRMP with other pathogens led to prolonged hospitalization and higher

laboratory-related indicators in patients. In addition, there was an increased incidence of pleural effusion, hepatic impairment, and complications of abnormal cardiac enzyme profiles. This requires clinicians to pay close attention to the changes in the patient's disease during the course of treatment in order to prevent complications from affecting the quality of life of the child.

Abbreviations

ALT: Alanine aminotransferase, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, CAP: community-acquired pneumonia, CK: creatine kinase, COVID-19: Coronavirus Disease 2019, CRE: creatinine, CRP: C-reactive protein, DD: D-dimer, EBV: Epstein-Barr virus, eGFR: estimated glomerular filtration rate, FDP: fibrinogen degradation product, FIB: fibrinogen, FMPP: fulminant *Mycoplasma pneumoniae* pneumonia, ICU: Intensive Care Unit, LDH: lactate dehydrogenase, LYM: lymphocyte, MON: monocytes, MP: *Mycoplasma pneumoniae*, MPP: *Mycoplasma pneumoniae* pneumonia, MRMP: macrolide-resistant *Mycoplasma pneumoniae*, NEU: neutrophils, PCT: procalcitonin, PLT: platelet count, PT: prothrombin time, RMPP: refractory *Mycoplasma pneumoniae* pneumonia, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, SMPP: severe *Mycoplasma pneumoniae* pneumonia, TP: total protein, TT: thrombin time, UA: uric acid, UREA: urea, WBC: white blood cell count.

Author Contributions

Zhengyuan Wang conceived the project and collect clinical data. Zhengyuan Wang performed data analysis and wrote the initial manuscript. Yuanhong Xu provided useful advice regarding the manuscript. All authors read and approved the final manuscript.

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Funding Information

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Ethics Approval and Consent to Participate

The current investigation was duly approved by the human ethics council of Anhui Medical University's First Affiliated Hospital (Approval No: Quick-PJ 2023-08-41). The written informed consent was obtained from patients in accordance

with the Declaration of Helsinki.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

All data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

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