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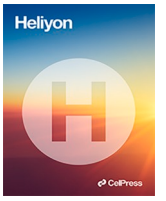

Research article

Macrolide-resistant *mycoplasma pneumoniae* infection in children observed during a period of high incidence in Henan, China

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ABSTRACT

Objective: Mycoplasma pneumoniae (Mp) is one of the major pathogens that causes respiratory tract infections, and macrolide resistance has increased rapidly in recent years due to the inappropriate use of macrolides in northeastern Asia. In the present study, we aimed to investigate Mp infection and macrolide resistance during a period of high incidence of Mp infection in Henan, China.
Methods: A total of 29473 suspected children with Mp infection were enrolled in the study from July to December 2023. Throat swab specimens were collected from all the study subjects, and real-time PCR was performed to detect the Mp-DNA and macrolide resistance-associated A2063G or A2064G mutations.
Results: The overall percentage of Mp-DNA-positive patients was 51.1 %, and the percentage of macrolide-resistant strains was 91 %. The rate of macrolide resistance remained stable from July to December. The Mp-DNA positivity rates among the different age groups from low to high were 0–1, 1–3, 3–6, 10–18 and 6–10 years. The macrolide resistance rate was the lowest in the 0–1 age group and highest in the 6–10 age group. No difference in the rate of macrolide resistance was observed between male and female children.
Conclusions: The macrolide resistance rate of Mp did not change during the investigated period of high incidence of infection, and no sex difference existed. The macrolide resistance rate of Mp was the lowest in children under 1 year old.

1. Introduction

Mycoplasma pneumoniae (Mp) is one of the leading causes of respiratory infections and community-acquired pneumonia (CAP) and accounts for 10–40 % of CAPs [1]. Mp infection can affect people of any age but is most common among children and adolescents. The clinical symptoms of Mp infection can include sore throat, fatigue, fever, cough and headache. In addition to respiratory symptoms, Mp infection can affect the skin, mucosa, liver and central nervous system [2]. Mp infection can occur at any time of year but may be more common in autumn and winter. The outbreak of Mp infection cycles at 3–7 years [3], and the pathogens are transmitted mainly through droplets.

Due to the absence of cell walls, Mp is inherently resistant to β-lactam antibiotics. Macrolides are the first-line treatment drugs for Mp infection in children due to slight side effects. Because of the excessive and inappropriate use of macrolides in recent years, infections with macrolide-resistant Mp (MRMP) have appeared and increased rapidly in northeastern Asia, and the macrolide resistance

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rate could reach 80–100 % in China, Japan and South Korea [4–7]. However, the prevalence of MRMP has remained relatively stable in the majority of European countries and North America over years [8–11]. Studies have shown that macrolide resistance in Mp is associated with a single point nucleotide mutation in region V of the 23S rRNA gene [12]. These mutations can cause macrolide resistance by reducing the ability of macrolides to bind to 23S rRNA; thus, the inhibitory ability of macrolides decreases due to decreased inhibition of Mp protein synthesis. The macrolide resistance-associated single point mutations mainly occur at sites 2063, 2064, 2617 and 2067, among which A2063G is the most frequent mutation, followed by A2064G, accounting for the vast majority of the total mutations [13–16]. In China, only mutations at sites 2063 and 2064 have been identified [17,18]; therefore, it is reliable to test A2063G and A2064G for the diagnosis of MRMP infection in China.

The present methods for the diagnosis of Mp infection in clinical laboratories include culture, molecular methods and serologic tests, and the molecular methods used refer to real-time PCR (RT–PCR) tests [19]. Macrolide resistance-associated mutations could be detected by sequencing and RT−PCR tests of region V of the 23S rRNA gene. The sequencing method is more accurate for detecting macrolide resistance-associated mutations than other methods, but it is time consuming and more expensive. RT−PCR methods targeting the A2063G and A2064G mutations can be inexpensive and rapid for the diagnosis of MRMP infection. Therefore, RT−PCR is practicable for the clinical diagnosis of MRMP infections.

In recent years, the SAR2-CoV-2 pandemic has changed the etiology landscape of respiratory infections in children, including the prevalence of Mp infection [20–23]. In the study by Ma et al., a statistically significant decreased trend of Mp infection was observed in the pandemic year in children in Henan Province, China, compared with that in the years before COVID-19, which might be caused by the measures taken to control the pandemic [23]. In the post-COVID-19 era, a high incidence of Mp infection has been reported in China, Colombia and European countries including Spain, France and Denmark in the year of 2023; this infection affected the health not only in children but also in adults and placed serious burden on the healthcare institutions [24–27]. The incidence of Mp infection started to increase in June in China, February in Colombia and October in Europe. Our study focused on this period of high incidence of Mp infection in children in Henan Province, China, and we studied the infection and macrolide resistance rates of Mp through different months, among different ages of children and between different sexes, which will provide a deep understanding of this wave of Mp infection.

2. Methods

2.1. Study subjects

Children who visited outpatient care or were hospitalized because of suspected Mp infection at the Children's Hospital Affiliated to Zhengzhou University from July to December 2023 were enrolled in the study. The suspected symptoms of Mp infection included fever, cough and headache. All the included subjects were tested for Mp infection, and the Mp-positive patients were tested for macrolide resistance at the same time. The study subjects were grouped based on age: 0–1, 1–3, 3–6, 6–10, and 10–18 years. Mp infection and macrolide resistance were also compared among different months and between the sexes.

2.2. Mp infection and macrolide resistance tests

Throat swab specimens were collected from all the children, and the specimens were then put into preserving fluid (DAAN GENE, Guangzhou, China). The active component of the preservation solution contains guanidine salt, which can denature the protein structure of cells or viruses and inactivate viruses or other microorganisms. The tubes were oscillated several times to allow the specimens to mix with the liquids completely. DNA was extracted from the liquids with qualified DNA extraction kits (Zybio, China), and the extracted DNA was subjected to RT−PCR tests of Mp infection and macrolide resistance-associated mutations.

Mp infection and macrolide resistance-associated mutations were tested with commercialized Mp nucleic acid and macrolide

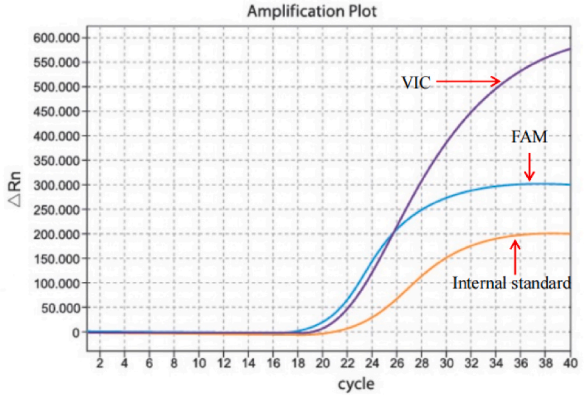

Fig. 1. Amplication plots of the Mp *p*1 gene and macrolide resistance-associated mutations in the 23S rRNA gene.

resistance mutation point detection kits from Mole (Jiangsu, China). Mp infection was diagnosed via RT−PCR of the *p1* gene in the Mp genome, and macrolide resistance-associated mutations were detected via RT−PCR targeting the A2063G and A2064G mutations of the 23S rRNA gene. The method could detect *p1* gene and macrolide resistance-associated mutations in 23S rRNA gene completely at 5000 copies/mL, and it had a detection limit of 500 copies/mL. The reaction volume of the PCR is 25 μL, so the method could detect *mycoplasma pneumoniae* and the mutations associated with macrolide resistance completely at 125 copies per test, and could detect 13 copies per test. RT−PCR was performed as follows: 1 cycle (50 °C, 2 min); 1 cycle (95 °C, 2 min); and 40 cycles (91 °C, 15 s and 64 °C, 1 min). Mp-DNA and macrolide resistance-associated mutations in the 23S rRNA gene were detected by amplification curves, and the VIC and FAM fluorescence amplification curves with Ct < 35 represented the positive results of Mp-DNA and macrolide resistance-associated mutations respectively (see Fig. 1). However, the detection method was limited to distinguishing between the known transitions at positions 2063/2064 of region V of the 23S rRNA gene.

2.3. Statistical analysis

For qualitative data, the chi-square test was performed for comparisons, and the Bonferroni method was used for further comparisons between two groups. $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Mp infection and macrolide resistance during different months

In this study, a total of 29473 patients were recruited within six months of 2023, 15051 (51.1 %) of whom were positive for Mp infection and 13695 (91 %) of the strains were macrolide resistant. The numbers of Mp-DNA-positive patients and macrolide-resistant strains and the rates of Mp-positive patients and macrolide-resistant strains in each month are shown in Table 1. No significant difference existed in the rates of macrolide resistant strains among the different months ($P = 0.024$). There was no significant difference in the percentage of Mp-DNA-positive patients between August and December or between October and November, but the percentages of Mp-DNA-positive patients were significantly different between any of the other two months.

The numbers of Mp-DNA-positive patients and macrolide-resistant strains and the rates of Mp infection and macrolide resistance in different age groups are shown in Table 2. The number of children enrolled in each group was greater than 2000, the lowest number was 2306 in the 0–1 age group, and the highest number was in the 6–10 age group, with 11846 children. The Mp infection positivity rates were significantly different between any two age groups of children, and the highest and lowest rates were in the 6–10 and 0–1 age groups, with rates of 68.6 % and 13.8 %, respectively. Except for those in the 0–1 age group, the rates of macrolide resistant strains in the other age groups were approximately equal to the total positive rate. According to the statistical results, the macrolide resistance rate was the lowest in the 0–1 age group and highest in the 6–10 age group, with rates of 61.1 % and 92.9 %, respectively. No significant difference in rates of macrolide resistant strains was observed among the 1–3, 3–6 and 10–18 age groups.

Mp infection and macrolide resistance in male and female children.

The numbers of enrolled patients, Mp-infected patients and macrolide resistant strains, and the rates of Mp-positive cases and macrolide resistance of male and female children are shown in Table 3. The percentage of Mp-DNA-positive female children was significantly greater than that of male children ($P < 0.01$), while there was no significant difference in macrolide resistance between male and female children.

4. Discussion

Currently, studies on MRMPs worldwide have been concentrated mainly in North America, European countries, Japan, South Korea, and China, while Chinese studies were mainly performed in Beijing and few studies have been published about MRMPs in the central provinces of China. In the present study, we investigated the rates of Mp infection and macrolide resistance during a period of high incidence of Mp infection in Henan Province, the central part of China. The *p1* gene was tested for Mp infections, and macrolide resistance was identified by RT−PCR tests of the A2063G and A2064G mutations. In comparison to previous studies about MRMP in China and reported studies about this current trend of high incidence of MRMP, we enrolled a much larger number of Mp and MRMP

Table 1
The number of Mp-DNA-positive patients and macrolide-resistant strains during different months.

Month	Number of tested cases	Number of Mp positive cases	Mp positive rates (%)	Number of macrolide resistant stains	Rate of macrolide resistant strains (%)
July	1419	299	21.1_a	277	92.6
August	2571	1029	40.0_b	914	88.8
September	3500	1623	46.4_c	1456	89.7
October	6895	4224	61.3_d	3874	91.7
November	8496	5093	59.9_d	4636	91.0
December	6592	2783	42.2_b	2538	91.2
Total	29473	15051	51.1	13695	91.0

Mp infection and macrolide resistance in different age groups of children.

Table 2
The number of Mp-DNA-positive patients and macrolide-resistant strains in different age groups.

Age groups	Number of tested cases	Number of Mp positive cases	Mp positive rates (%)	Number of macrolide resistant strains	Rate of macrolide resistant strains (%)
0–1	2306	319	13.8_a	195	61.1_a
1–3	3711	931	25.1_b	824	88.5_b
3–6	8039	3563	44.3_c	3222	90.4_b
6–10	11846	8122	68.6_d	7543	92.9_c
10–18	3582	2116	59.1_e	1911	90.3_b

Table 3
The results of the Mp-DNA and macrolide resistance tests between different sexes.

Sex	Number of tested cases	Number of Mp positive cases	Mp positive rates (%)	Number of macrolide resistant strains	Rate of macrolide resistant strains (%)
Male	16395	8156	49.7[a]	7402	90.8
Female	13079	6895	52.7[a]	6293	91.3

[a] $P < 0.01$.

strains infecting children in our study, which included 15051 Mp and 13695 MRMP strains. The macrolide resistance rate of Mp (91 %) was also much greater in our study than in European countries during this trend [11]. A much greater rate of Mp infection was observed in our study than in the pandemic years (2020 and 2021) and the years before COVID-19 (2018 and 2019) in children in Henan Province [23]. The application of RT−PCR improved the efficiency of the clinical tests of Mp and MRMP in our study. The Children's Hospital Affiliated to Zhengzhou University is the central Hospital for children in Henan Province, and Henan has nearly 100 million people and millions of children, which laid the foundation for the large number of study subjects included in the six-month study. However, in comparison to the studies by Xu et al. [28], Zhao et al. [29] and Sun et al. [17], which focused on the study of macrolide resistance of Mp through several years, the period included in our study was only six months. Zhao et al. reported that the macrolide resistance rates of Mp in 2014, 2015 and 2016 in Beijing were 59.3 %, 73.7 % and 65.7 % respectively [29], and the macrolide resistance rate of Mp in our study remained stable over six months. Therefore, further studies are needed for the continuous surveillance of macrolide resistance in Mp in Henan, China (see Fig. 2).

In terms of the epidemiology of MRMP in different regions of the world, the incidence rates of MRMP are higher in Asian countries, especially in China, Japan and South Korea; however, the incidence rate of MRMP is lower in America and European countries, where the incidence rate is usually less than 10 % (except Italy), and the incidence rate of MRMP in Italy is approximately 26 % [8,30–32]. In our study, we observed a relatively high macrolide resistance rate of 91 % in Henan, China. In a study by Zhao et al., which was performed in 5 cities in China between January 2017 and December 2018, the macrolide resistance rates of Mp in different cities varied: 100 % (Jilin), 66.7 % (Beijing), 54.5 % (Jinan), 91.7 % (Suzhou) and 75 % (Fuyang) [13]. Xu et al. reported a macrolide resistance rate of 96 % in Wuhan city from 2020 to 2022 [28], and Zhou et al. reported a 100 % macrolide resistance rate in Zhejiang

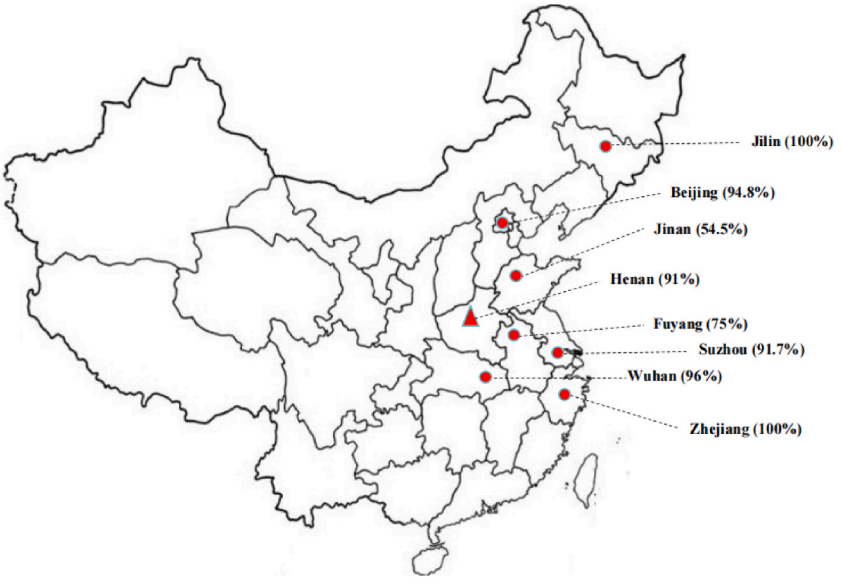

Fig. 2. The macrolide resistance rates in different regions of mainland China.

Province, China, from January 2012 to August 2014 [7]. The percentages identified in the studies by Dou HW et al., in 2016 and Sun H et al. in 2003–2015 in Beijing, China were 66 % and 94.8 % respectively [17,18]. The positions of the above listed regions in China and the macrolide resistance rates of Mp are shown in Fig. 2. It can be concluded that macrolide resistance rates can differ across different regions of China, and the macrolide resistance rate of Mp in Henan is close to that in Suzhou and Wuhan. The data about the rates of macrolide resistance of Mp are deficient in the majority of regions of mainland China, so further investigations are required in future studies.

In the present study, we also investigated the epidemiology of MRMP among different age groups and between different sexes. With regard to age, we found a significantly lower rate of macrolide resistance in children under 1 year of age and a significantly greater rate of macrolide resistance in children aged 6–10 years. In contrast to our study, another study conducted in Japan by Kawakami et al. reported no significant difference in the prevalence of MRMP among different age groups of children [33]. However, the children in the study by Kawakami were divided into preschool-aged children (≤5 years), school-aged children (6–15 years) and adolescents (16–19 years), which is different from the grouping method of our study and might contribute to the different results of the prevalence of MRMP in different age groups of children. We found no significant difference in the ratio of macrolide resistance between male and female children, which was consistent with the findings of the study by Waites et al. [34].

Interestingly, the rate of macrolide resistance in children in the 0–1 age group was markedly lower than that in the other age groups. The reasons for the low rate of macrolide resistance in children in the 0–1 age group are unknown. Kawakami et al. reported a statistically greater prevalence of macrolide resistance-associated mutation-positive Mp in patients previously treated with macrolides than in patients without macrolide treatment [33]. Therefore, macrolide resistance of Mp in patients could develop during the frequent use of macrolides [35]. Children in the 0–1 age group might suffer fewer Mp infections, and it is very likely that children under 1 year of age had never been infected by Mp before this study, which led to less macrolide antibiotic use to allow the development of macrolide resistance in Mp. The low rate of macrolide resistance in neonates may be of clinical significance for the benefit of using macrolides in treatment and reducing the adverse effects of other alternative treatments.

There may be several limitations to our study. First, strain typing was not performed for the molecular studies of Mp. Second, no clinical presentation of the Mp-infected patients was included in the analysis. Third, this was a one-site study of Mp infection and macrolide resistance. Finally, only mutations at sites 2063 and 2064 in the V region of 23S rRNA were detected to indicate macrolide resistance in Mp and the possible existence of other sites associated with macrolide resistance was not detected.

Conclusion

According to our study, the incidence of MRMP is very high in Henan Province, China. The rate of MRMP did not change during the investigated period of high incidence of Mp infection; the prevalence of MRMP was markedly lower in children younger than 1 year of age; the incidence of MRMP was not significantly different according to sex.

Ethical approval

This retrospective study was approved by the Ethics Committee of Henan Children's Hospital (2024-K-041). Informed patient consent was waived.

Funding

No.

Data availability statement

As a retrospective study, the data associated with the study has not been deposited into a publicly available repository. Key data is included in the tables of the article, and raw datasets are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Maodong Leng: Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Junmei Yang:** Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xinrui Liu:** Methodology, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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