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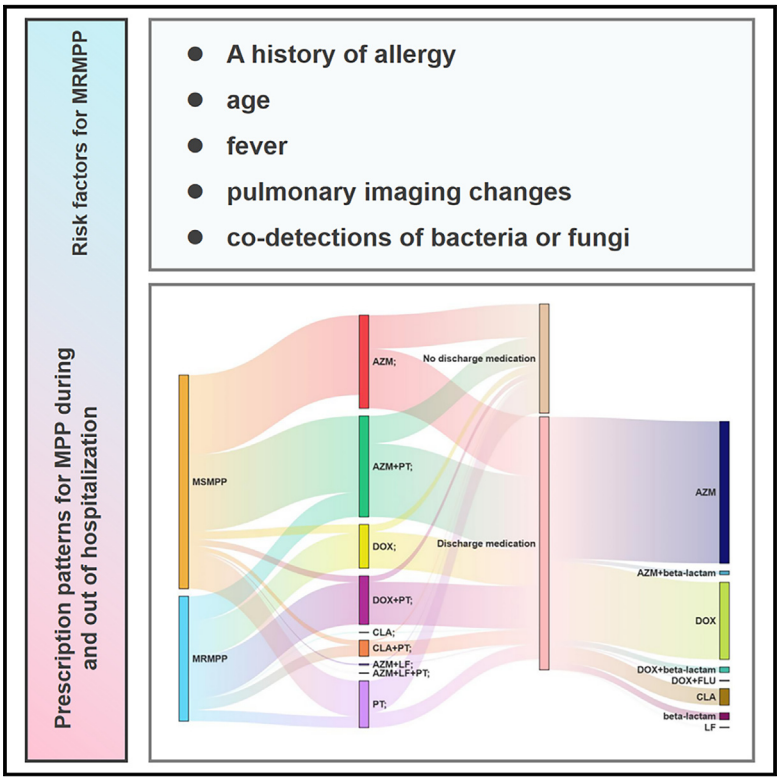
Risk factors and prescription patterns analysis for macrolide-resistant Mycoplasma pneumoniae pneumonia in children

Graphical abstract



Highlights

- The MRMPP group had a longer fever duration compared to the MSMPP group
- MRMPP group mainly received doxycycline combined with piperacillin-tazobactam in the hospital
- A history of allergy emerged as an increased risk factor for MRMPP

Authors

Yun Lu, Wen-jing Li, Xuan-xuan Wang, An-qi Huang, Hong Cheng

Correspondence

chenghong@znhospital.cn

In brief

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Risk factors and prescription patterns analysis for macrolide-resistant Mycoplasma pneumoniae pneumonia in children

Yun Lu,[1,2] Wen-jing Li,[1,2] Xuan-xuan Wang,[1] An-qi Huang,[1] and Hong Cheng[1,3,*]
[1]Department of Pharmacy, Zhongnan Hospital of Wuhan University, Wuhan, China
[2]These authors contributed equally
[3]Lead contact
*Correspondence: chenghong@znhospital.cn
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SUMMARY

First-line macrolide therapy is encountering challenges due to the escalating incidence of macrolide-resistant Mycoplasma pneumoniae pneumonia (MRMPP). This study aimed to illustrate prescription patterns among children diagnosed with either macrolide-sensitive Mycoplasma pneumoniae pneumonia (MSMPP) or MRMPP and to further analyze the risk factors associated with MRMPP. This research encompassed 825 children who were diagnosed with Mycoplasma pneumoniae pneumonia (MPP) at a tertiary hospital located in central China in 2023. Notably, the MRMPP group had a longer fever duration compared to the MSMPP group. A combination of doxycycline and piperacillin-tazobactam was the most frequently used treatment for hospitalized MRMPP children, whereas azithromycin was the primary choice for the MSMPP group. More children in the MRMPP group required discharge medications, primarily doxycycline, whereas the MSMPP group primarily received azithromycin. Furthermore, a history of allergy emerged as an increased risk factor for MRMPP, alongside age, fever, pulmonary imaging changes, and co-detections of bacteria or fungi.

INTRODUCTION

Mycoplasma pneumoniae (MP) stands as one of the most commonly encountered pathogens in cases of community-acquired bacterial pneumonia among children.[1] MP infections are usually treated with macrolide antibiotics, such as azithromycin and clarithromycin, as the first line of treatment. Due to the increased use of macrolide antibiotics, the prevalence of macrolide-resistant Mycoplasma pneumoniae pneumonia (MRMPP), which is characterized by a poor response to these drugs, has increased. This may result in a discernible rise in the number of cases of severe and refractory Mycoplasma pneumoniae pneumonia (MPP), creating difficulties for clinical treatment.[2,3]

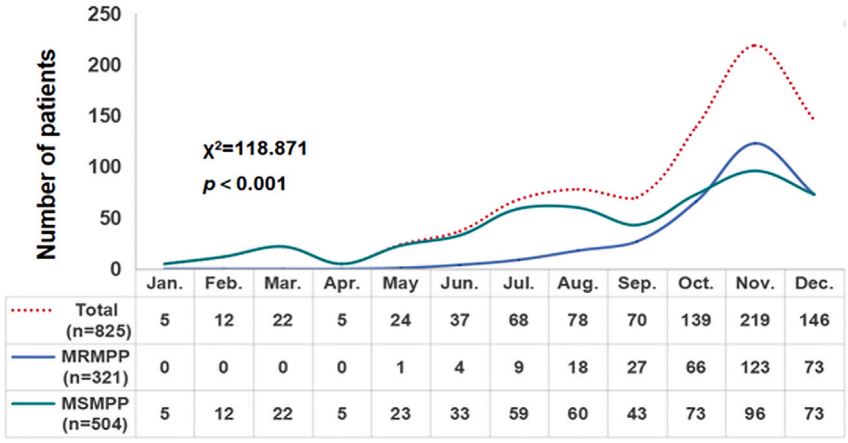
Previous research extensively focused on the A2063G and A2064G sites mutations in the domain V of the 23S ribosomal RNA gene of MP that can lead to reduced affinity between macrolide drugs and ribosomes, which accounts for the underlying resistance mechanism.[4,5] Although next-generation sequencing has facilitated the detection and diagnosis of MRMPP,[6] and guidelines have recommended the use of doxycycline and minocycline for its treatment, clinicians still encounter challenges in practice.[7–9] For instance, the initial treatment before the definitive diagnosis is not conclusive. Additionally, the use of doxycycline in children under 8 years old constitutes off-label use, necessitating the careful consideration of risks and benefits along with informed consent. Further, MP is often co-detected with other pathogens, posing a dilemma for clinicians regarding whether the combination of antimicrobial therapy is necessary since they may be colonized pathogen.[10,11] At present, there are few reports that delve into the prescription patterns of MPP. Therefore, it is necessary to analyze the treatment regimens of MPP and evaluate the risk factors for MRMPP in children.

In view of the worldwide re-emergence of MPP, including some provinces in China,[12–14] this study retrospectively analyzed the prescription patterns and risk factors of children diagnosed with MPP, in order to highlight the risk of MRMPP and severe complications and provide reference for appropriate management of the disease.

RESULT

Monthly distribution of children infected with Mycoplasma pneumoniae pneumonia

In this study, 825 children diagnosed with MPP were tested by targeted microbial next-generation sequencing (tNGS) at Zhongnan Hospital of Wuhan University in 2023. The samples tested were from blood, alveolar lavage fluid, or sputum. None of them required admission to the intensive care unit (ICU) or died. The number of cases and drug resistance of MP for each month in 2023 was reviewed in Figure 1, and the percentage of MRMP sequences reported by tNGS were shown in Table S1. In early 2023, the number of pediatric patients hospitalized with MPP was comparatively minimal. Nonetheless, an increase was evident commencing from July, culminating in November ($\chi 2 = 118.871$, $p < 0.001$).



	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Total (n=825)	5	12	22	5	24	37	68	78	70	139	219	146
MRMPP (n=321)	0	0	0	0	1	4	9	18	27	66	123	73
MSMPP (n=504)	5	12	22	5	23	33	59	60	43	73	96	73

Figure 1. Monthly distribution of children with MPP throughout 2023 in the Zhongnan Hospital of Wuhan University

Macrolide-resistant Mycoplasma pneumoniae pneumonia, MRMPP; macrolide-sensitive Mycoplasma pneumoniae pneumonia, MSMPP.

Demographic and clinical characteristics of children with Mycoplasma pneumoniae pneumonia

Demographic information, clinical characteristics at admission, medical history, co-detection, supportive treatments during hospitalization, costs and outcomes were described in Table 1. Macrolide-resistant genes of MP were detected in 321 children. In the MRMPP group, there were more male children, older age, and more with food and drug allergy history. Breastfeeding, full-term infants, and MP infection history had no significant effects. Compared with the MSMPP group, more children in the MRMPP group showed cough, fever, and pulmonary imaging changes and were more likely to be co-detected with bacteria and fungi. The co-detected bacteria detected were mainly represented by Streptococcus pneumoniae, *Staphylococcus aureus*, and *Escherichia coli*. Fungi were represented by candida. The virus was represented by influenza virus and COVID-19. Only a small number of children were detected with respiratory syncytial virus (RSV) and rhinovirus (data not shown). There was a significant difference in the proportion of children receiving supportive treatment. More children in the MRMPP group were prescribed corticosteroids and oxygen inhalation. Days of hospital stay and disease course were comparable, but the children in the MRMPP group had longer fever days and higher medical costs.

Antimicrobial prescription patterns of children with Mycoplasma pneumoniae pneumonia

The total number of drug use and antimicrobial prescription patterns during the hospitalization of children with MPP was shown in Table 2. First, children in the MRMPP group used more medication compared with the MSMPP group (18.00 ± 7.00 vs. 15.00 ± 6.75). In the MRMPP group, the most frequently prescribed antibiotic regimen for children was "DOX+PT" (28.66%), whereas in the MSMPP group, "AZM alone" was the most administered (34.52%). Besides, "DOX alone" (23.99%) and "AZM+PT" (16.82%) in the MRMPP group, as well as "AZM+PT" (32.94%) and "PT alone" (15.48%) in the MSMPP group were also common regimens.

Besides, the total fever days between the two groups of children under different medication patterns were compared, and it was found that children who received AZM alone or PT alone had longer fever days in the MRMPP group (Table 3). There were also significant differences in discharge medications medication between the two groups. In the MRMPP group, nearly 79.13% of children received discharge medications, with DOX alone accounting for the majority of treatments (45.79%). In comparison, 48.61% of the MSMPP group were mostly prescribed with AZM (Table 4). Prescription patterns both during hospitalization and after discharge were shown by the Sankey diagram in Figure 2.

Multivariate logistic regression analysis of macrolide-resistant Mycoplasma pneumoniae pneumonia

The results of multivariate logistic regression analysis showed that age (OR = 2.67, 95% CI: 1.89–3.78; $p < 0.001$), history of allergies (OR = 1.74, 95% CI: 1.14–2.65; $p = 0.011$), fever (OR = 3.38, 95% CI: 1.24–9.18; $p = 0.017$), pulmonary imaging changes (OR = 7.17, 95% CI: 2.14–24.07; $p = 0.001$), co-detection with bacteria (OR = 3.21, 95% CI: 2.27–4.54; $p < 0.001$), and co-detection with fungi (OR = 5.22, 95% CI: 1.97–13.82; $p = 0.001$) were all risk factors associated with the MRMPP (Figure 3).

DISCUSSION

The number of children visiting clinics has decreased globally since the COVID-19 outbreak in 2020, possibly as a result of non-pharmaceutical interventions such as wearing masks, reducing the frequency of outdoor activities and travel, and using online education at home, which have not only successfully stopped the spread of the virus but also decreased a variety of respiratory pathogenic infections.[15,16] China has designated COVID-19 as a category B infectious illness at the beginning of 2023, while at the end of 2023, MP replaced the status of respiratory viruses that were prone to prevalence during autumn and winter.[17] Early diagnosis and effective pharmacological treatment contributed to reducing the transmission of MP; however, treatment protocols for pediatric MPP in hospitals exhibit considerable diversity. It is meaningful to illustrate the prescription patterns of MPP children in China.

This study included 825 children diagnosed with MPP in our hospital in 2023. From January to April, fewer than 30 children were diagnosed with MPP. Beginning in May, cases of MRMP were progressively identified. Notably, from September onwards, there was a significant surge in the number of children diagnosed with both MPP and MRMPP, with the detection rate of MRMPP peaking in November at 56%. However, the detection rates of MP and MRMP declined in December. Several studies have reported a global increase in the proportion of

Table 1. Demographic and clinical characteristics of children with MPP

Variables	Total (*n* = 825)	MRMPP (*n* = 321)	MSMPP (*n* = 504)	*p* value
Demographic character				
Male gender, n (%)	423 (51.27)	181 (56.39)	242 (48.02)	0.019
Age, months, median (IQR)	85.17 (57.59–109.73)	91.97 (76.43–112.25)	78.29 (44.67–107.65)	<0.001
Full-term infant, n (%)	754 (91.39)	301 (93.77)	453 (89.88)	0.052
Breastfeeding, n (%)	633 (76.73)	249 (77.57)	384 (76.19)	0.648
Clinical characteristics at admission, n (%)				
Cough	783 (94.91)	320 (99.69)	463 (91.87)	<0.001
Fever	763 (92.48)	315 (98.13)	448 (88.90)	<0.001
Pulmonary imaging changes	747 (90.55)	318 (99.07)	429 (85.12)	<0.001
Medical history, n (%)				
MP infection history	20 (2.42)	8 (2.49)	12 (2.38)	0.919
Allergy history	137 (16.61)	69 (21.50)	68 (13.49)	0.003
Pathogens co-detected with MP, n (%)				
None	225 (27.27)	58 (18.07)	167 (33.13)	<0.001
Bacteria	235 (28.48)	142 (44.24)	93 (18.45)	<0.001
Influenza virus	464 (56.24)	186 (57.94)	278 (55.16)	0.432
Fungi	35 (4.24)	29 (9.03)	6 (1.19)	<0.001
COVID-19	14 (1.70)	5 (1.56)	9 (1.79)	0.805
Supportive treatments during hospitalization, n (%)				
Corticosteroids	571 (69.21)	270 (84.11)	301 (59.72)	<0.001
Immunoglobulin	2 (0.24)	2 (0.62)	0 (0.00)	0.373
Low molecular heparin	14 (1.70)	6 (1.87)	8 (1.59)	0.204
Oxygen inhalation	310 (37.58)	166 (51.71)	144 (28.57)	<0.001
Cost, yuan, median (IQR)				
Total cost	4628.12 (3787.38–6524.86)	5354.64 (4086.43–6719.78)	4382.53 (3657.12–6229.32)	<0.001
Daily cost	891.67 (712.70–1140.63)	976.66 (766.10–1206.09)	854.23 (691.29–1082.52)	<0.001
Outcomes, days, median (IQR)				
The onset of symptoms to hospital admission	7.00 (5.00–9.00)	7.00 (6.00–9.00)	7.00 (5.00–8.00)	0.107
Length of hospital stay	5.00 (5.00–7.00)	5.00 (5.00–6.00)	5.00 (5.00–7.00)	0.144
Disease course	13.00 (11.00–15.00)	13.00 (11.00–15.00)	13.00 (10.00–15.00)	0.918

MRMPP, Macrolide-resistant Mycoplasma pneumoniae pneumonia; MSMPP, Macrolide-sensitive Mycoplasma pneumoniae pneumonia.

MRMPP,[18] with rates reaching 90% in some Chinese provinces.[19,20] Nevertheless, the average detection rate of MRMP in our hospital in 2023 was comparatively lower, accounting for 38.9%. Given China's vast territory and significant climatic differences between the north and south, variations in the detection rates of MP resistance do exist, even among neighboring provinces. Consequently, geographical differences may be an inevitable and objective factor influencing these rates.[21]

Notably, our hospital and most domestic hospitals have implemented hierarchical diagnosis and treatment, consequently, the outpatient intravenous medications have been significantly reduced. Children with poor improvement in respiratory symptoms by family therapy will be further admitted to the hospital. Even though the guidelines clearly recommend drug therapy for MPP, clinical practice still needs to consider modifying treatment plans and drug combinations when necessary. The initial antibiotic therapy in a hospital is always based on empirical judgment due to the unknown causative pathogen.[22] Children who were diagnosed or suspected with MPP via clinical symptoms or pulmonary imaging changes would be treated with macrolide drugs which are the first choice of monotherapy for MPP. Sometimes the results of tNGS may be reported a few days later. If the macrolide treatment was effective, though the MRMP was detected, the monotherapy of the macrolide drug will be continued. In this study, we divided the cohort into MRMPP and MSPPP groups based on the tNGS reports. However, different drug-resistant genes contribute differently to drug resistance phenotypes. Besides, the causal relationship between the drug-resistant genes and the resistance of the samples has not been totally confirmed.[23] Therefore, the detection of MRMPP does not necessarily mean that macrolide drugs are completely ineffective. In addition, when the percentage of MRMP sequences is low, macrolide drugs are still effective, "macrolides alone" is also a choice for MRMPP treatment. Similarly, for the MSMPP group, some children also received combined antimicrobial regimens when the children still had persistent fever or if the signs and pulmonary imaging changes did not improve or worsen after 72 h of treatment with macrolide alone.

Table 2. Prescribed antibiotics during the hospitalization of children with MPP

Variables	Total (*n* = 825)	MRMPP (*n* = 321)	MSMPP (*n* = 504)	*p* value
Total number of drug use, mean ± SEM	16.00 ± 8.00	18.00 ± 7.00	15.00 ± 6.75	<0.001
Number of children under different prescribed antibiotics, n (%)				
None	59 (7.15)	20 (6.23)	39 (7.74)	0.413
AZM alone	203 (24.61)	29 (9.03)	174 (34.52)	<0.001
AZM+PT	220 (26.67)	54 (16.82)	166 (32.94)	<0.001
AZM+LF	3 (0.36)	0 (0.00)	3 (0.60)	0.166
AZM+PT+LF	1 (0.12)	0 (0.00)	1 (0.20)	0.425
DOX alone	95 (11.52)	77 (23.99)	18 (3.57)	<0.001
DOX+PT	106 (12.85)	92 (28.66)	14 (2.78)	<0.001
CLA alone	1 (0.12)	1 (0.31)	0 (0.00)	0.210
CLA+PT	35 (4.24)	24 (7.48)	11(2.18)	<0.001
PT alone	102 (12.36)	24 (7.48)	78 (15.48)	0.001

MRMPP, Macrolide-resistant Mycoplasma pneumoniae pneumonia; MSMPP, Macrolide-sensitive Mycoplasma pneumoniae pneumonia; None, No antibiotics were used during hospitalization; AZM, Azithromycin; PT, Piperacillin-tazobactam; DOX, Doxycycline; CLA, Clarithromycin; LF, Levofloxacin.

Various guidelines suggest penicillins or cephalosporins that include enzyme inhibitors for the treatment of pneumonia, in which piperacillin-tazobactam has been recommended as a safe and effective choice for children which can provide more comprehensive coverage against potential pathogens to treat community-acquired pneumonia, hospital-acquired pneumonia, and infection of unknown source.[24,25] In this study, MSMPP children were mainly treated with azithromycin, whereas MRMPP children were mainly treated with doxycycline-based medications, frequently in conjunction with piperacillin-tazobactam. We noticed that a small number of children were treated with levofloxacin. In our hospital, informed consent is required from parents for the use of doxycycline in children under 8 years old and levofloxacin in children under 18 years old.

In addition, we also found the application of corticosteroids as supportive treatments for MPP especially in the MRMPP group. It has been reported that either macrolide susceptible or resistant, corticosteroids could be used in conjunction with suitable antimicrobials,[26] which may have promising efficacy in managing refractory MPP[27] to prevent disease progression,[28] although there is no consensus for the optimized dosage and duration of corticosteroid treatment so far. Besides, during and after the administration of corticosteroids, neither clinical presentations nor pulmonary imaging changes exhibited worsening upon the discontinuation of corticosteroid treatment, and no patients manifested any further complications attributable to infection.[9,29] In this study, methylprednisolone and prednisolone are the commonly used corticosteroids which have high safety when applied for a short course of treatment, and no serious adverse reactions caused by corticosteroids were observed.

In this study, some patients were tested only once for routine blood tests and pulmonary imaging tests during their hospitalization and did not follow up regularly after discharge or follow-up at other hospitals. Therefore, our study did not use the effect of anti-infection as the primary outcome. According to our single-center data, children diagnosed with MRMPP typically

Table 3. Total fever days under different prescribing patterns during the hospitalization in MRMPP and MSMPP groups

Variables	Total (*n* = 825)	MRMPP (*n* = 321)	MSMPP (*n* = 504)	*p* value
Total fever days, median (IQR)	5.00 (3.00–7.00)	6.00 (4.00–8.00)	4.00 (2.00–7.00)	<0.001
Total fever days under different prescribing patterns, median (IQR)				
None	4.00 (3.00–7.00)	4.00 (3.00–7.00)	4.00 (2.00–7.00)	0.910
AZM alone	5.00 (2.00–7.00)	7.00 (5.50–8.00)	4.00 (1.00–7.00)	<0.001
AZM+PT	5.00 (5.00–9.00)	6.00(4.00–8.25)	5.00(2.00–7.00)	0.056
AZM+LF	9.00(4.50–10.50)	/	9.00(4.50–10.50)	/
AZM+PT+LF	3.00	/	3.00	/
DOX alone	5.00 (4.00–7.00)	6.00 (4.00–7.00)	4.50 (2.75–7.25)	0.209
DOX+PT	7.00 (4.75–8.00)	6.50 (4.25–9.00)	7.00 (4.75–8.00)	0.397
CLA	11.00	11.00	/	/
CLA+PT	6.00 (4.00–8.00)	6.00 (4.25–8.00)	6.00 (4.00–8.00)	0.795
PT alone	5.00 (2.75–7.00)	6.00 (3.25–7.75)	4.00 (2.00–6.25)	0.032

MRMPP, Macrolide-resistant Mycoplasma pneumoniae pneumonia; MSMPP, Macrolide-sensitive Mycoplasma pneumoniae pneumonia; None, No antibiotics were used during hospitalization; AZM, Azithromycin; PT, Piperacillin-tazobactam; DOX, Doxycycline; CLA, Clarithromycin.

Table 4. Prescription patterns after discharge in MRMPP and MSMPP groups

Variables	Total (*n* = 825)	MRMPP (*n* = 321)	MSMPP (*n* = 504)	*p* value
None, n (%)	274 (33.21)	67 (20.87)	207 (41.07)	<0.001
Discharge medications, n (%)	551 (66.79)	254 (79.13)	297 (58.93)	<0.001
AZM alone	309 (37.45)	64 (19.94)	245 (48.61)	<0.001
AZM+beta-lactam antibiotics	8 (0.97)	3 (0.93)	5 (0.99)	0.935
DOX alone	168 (20.36)	147 (45.79)	21 (4.17)	<0.001
DOX+beta-lactam antibiotics	12 (1.45)	11 (3.43)	1 (0.20)	<0.001
DOX+FLU	2 (0.24)	2 (0.62)	0 (0.00)	0.076
CLA	36 (4.36)	26 (8.10)	10 (1.98)	<0.001
beta-lactam antibiotics	15 (1.82)	1 (0.31)	14 (2.78)	0.010
LF	1 (0.12)	0 (0.00)	1 (0.20)	0.425

None, No antibiotics were used after discharge; MRMPP, Macrolide-resistant Mycoplasma pneumoniae pneumonia; MSMPP, Macrolide-sensitive Mycoplasma pneumoniae pneumonia; AZM, Azithromycin; DOX, Doxycycline; FLU, Fluconazole; CLA, Clarithromycin; LF, Levofloxacin.

experience fever for a longer period of time than MSMPP children. Under some treatment regimens (azithromycin alone and piperacillin-tazobactam alone), the total fever days were shorter in the MSMPP group than in the MRMPP group. We did not observe a significant difference in the total fever days between various antimicrobial regimens in both the MSMPP group and the MRMPP group. Some studies suggested that doxycycline was significantly more effective in achieving defervescence within 24 h and in decreasing numbers of MPP DNA copies,[7,30] while some data have indicated that doxycycline does not show superior therapeutic effects compared to macrolide antibiotics.[31] We did not find any effect of doxycycline and azithromycin on the total fever duration in MPP children in this study which may be due to demographic and other variables. Besides, the combination of piperacillin-tazobactam did not reduce the duration of fever, which may be due to the fact that patients who use more antibiotics may experience more co-infections or co-detections. Thus, we cannot rule out the possibility that the combined use of antibacterial drugs may not have a significant effect on the duration of fever. In addition, fifty-nine pediatric patients did not receive antimicrobial therapy during their hospital stay. Although the reasons remained unknown, we speculated some possible factors such as a history of drug allergies or mild symptoms. There were also no significant differences in the total fever days between those who did not receive antimicrobial therapy. Therefore, we cannot simply compare the differences in total fever days to analyze the effects of different drug regimens, as fever is only one of the symptoms of MPP, and there were many confounding factors in our retrospective study.

It was interesting that both patients with MRMPP and MSMPP had comparable disease course as well as length of hospital stay which were objective parameters of disease severity. However, we cannot get the conclusion that there is no difference in severity between the two groups due to several factors. Firstly, the diagnosis-related groups (DRG) management has promoted patient turnover and reduced the length of hospital stay.[32] Secondly, although the detection of MRMPP indicates the severity of the disease to some extent, the actual treatment also takes into account the signs and symptoms so that severe patients receive more medications, while mild patients receive less medication or even no antimicrobial treatment. According to our data, patients with MRMPP had higher daily and total costs than patients with MSMPP, which may have an underlying effect on the length of hospital stay. Thirdly, discharge does not mean the end of treatment, patients with MRMPP were more likely to receive a prescription for doxycycline, while MSMPP children received azithromycin, and data also demonstrated that the proportion of patients who needed discharge medication was higher in the MRMPP group. Therefore, families and society may face much higher healthcare costs if MRMPP cases increase.

The tNGS testing was performed on every child in this study, which was essential for enabling an early diagnosis of MRMPP.[33] In our opinion, although the diagnostic efficacy of tNGS varies depending on the sensitivity and specificity, tNGS can serve as a complement to conventional microbiological tests in qualified medical institutions, and the effective combination of them can improve the level of diagnosis and treatment. A multivariate logistic regression analysis indicated that no significant correlation between gender and MRMPP, which was consistent with previous studies.[34,35] Our research revealed that age, history of allergy, fever, pulmonary imaging changes, and bacterial and fungal co-detection could be risk factors for MRMPP. The incidence of MRMPP increases with age, most likely due to cross-infection between school-age children and their classmates.[36,37] Fever and pulmonary imaging changes indicate disease progression and co-detections with bacterial and fungal, indicating more complications occur in MRMPP than in patients with MSMPP .[38] Our study was the first to demonstrate that a history of allergy was a risk factor for MRMPP. This finding was supported by similar studies that individuals with allergies were more susceptible to COVID-19 and that children who were allergic to penicillin were more likely to develop severe pneumonia.[39,40] Future research should focus on specific biomarkers and deep molecular mechanisms.

Strengths of the study

A strength of this study is that we have retrospectively reviewed and summarized the clinical information of pediatric patients with MPP in 2023. By categorizing the cases into MRMPP and

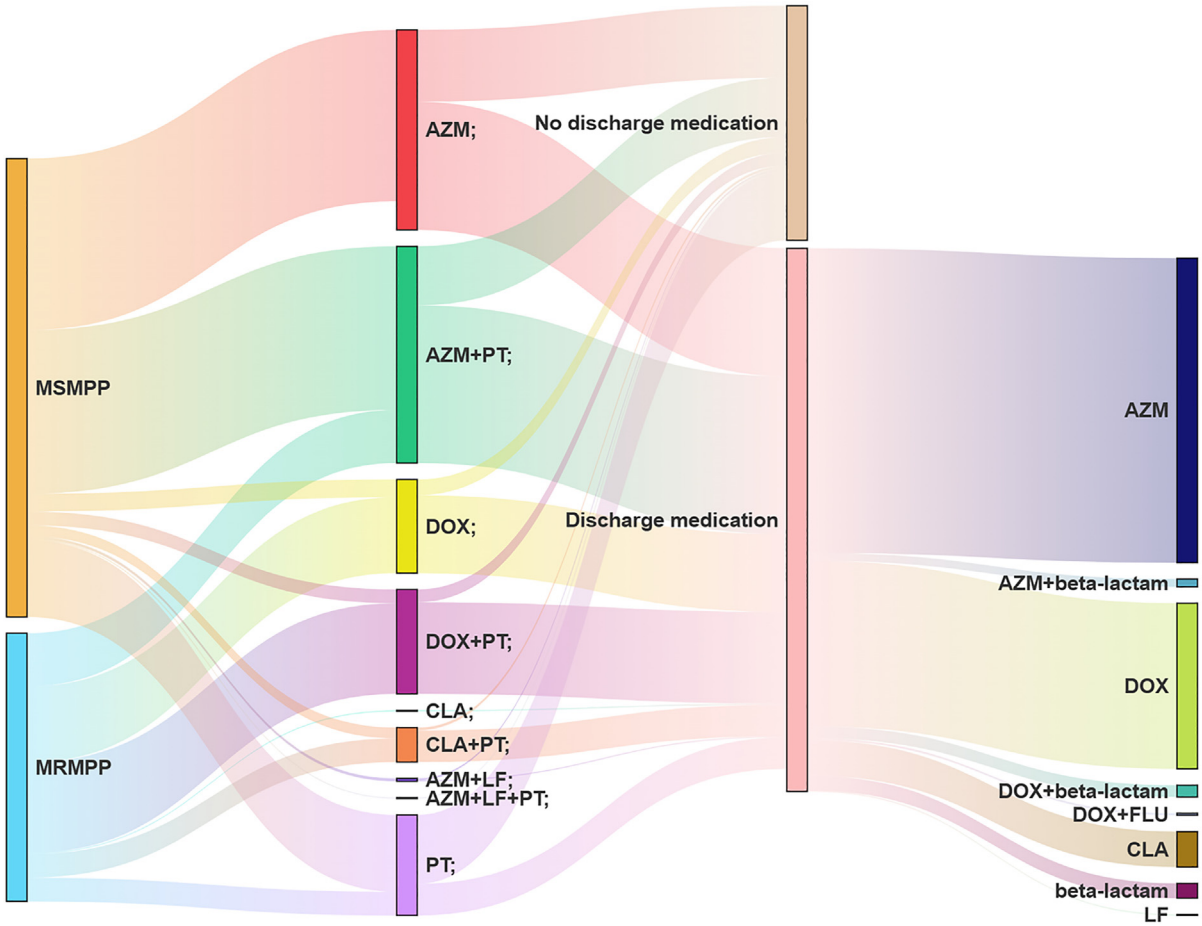


Figure 2. Prescription patterns during and out of hospitalization

Macrolide-sensitive Mycoplasma pneumoniae pneumonia, MSMPP; macrolide-resistant Mycoplasma pneumoniae pneumonia, MRMPP; azithromycin, AZM; piperacillin-tazobactam, PT; doxycycline, DOX; clarithromycin, CLA; levofloxacin, LF. Children do not need to continue using antibacterial drugs after discharge, No discharge medication. Anti-infective treatments for MP after discharge, Discharge medication.

MSMPP, we have described the distinct population characteristics and differences in medication patterns. Additionally, we have analyzed the risk factors for MRMPP infection, providing valuable clinical data to inform future diagnosis and treatment of the disease.

Limitations of the study

This study has several limitations. Firstly, as a single-center, retrospective study, it was constrained by a limited sample size and potential biases stemming from variations in medication practices. Secondly, pre-admission treatment data for the pediatric patients were not collected. Apart from a minority of patients with outpatient records from other hospitals, the majority of pre-admission medication information was gathered through parental interviews, making it challenging to ensure the accuracy and completeness of this data. Lastly, due to the study's non-randomized, controlled trial design, there were several confounding variables. The treatment regimens for patients with MPP were not standardized. Our primary focus was on describing the antimicrobial treatment patterns for MP and identifying risk factors for MRMPP, without comparing the efficacy of different treatment regimens.

Conclusions

MRMPP may be predicted by risk factors such as age, fever, pulmonary imaging changes, allergy history, and co-detection with bacteria or fungi. For the treatment of MPP, the drugs currently used in our hospital are basically in line with the recommended guidelines. However, there have indeed been many cases where a combination of antimicrobial drugs was used, which has also been a concern that our clinical pharmacists have been paying attention to. We will recommend minimizing the use of antimicrobial drug combinations, as no significant advantages were identified in this study. Pharmacy administration, particularly the management of antibacterial drugs, is an ongoing task that necessitates the translation of clinical data into compelling clinical evidence. Our primary objective in conducting this study was to delineate the existing prescription patterns, thereby offering a valuable reference for future clinical decisions and establishing a foundation for hospital pharmacy administration.

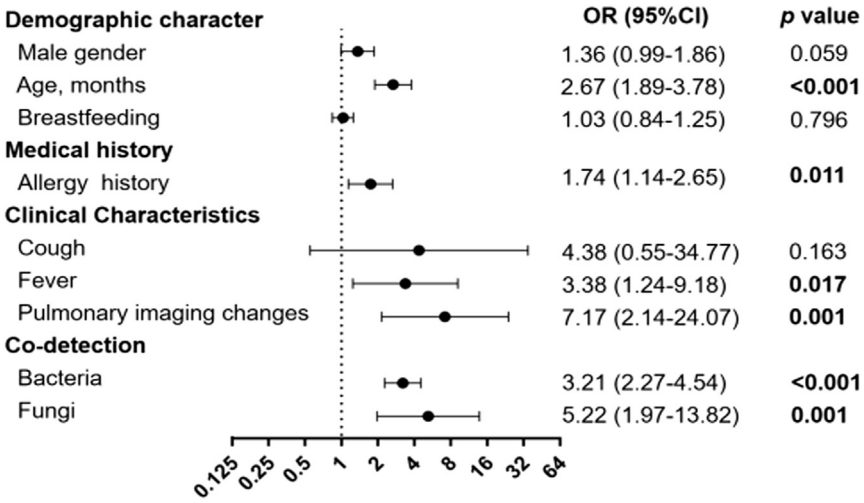


Figure 3. Multivariate logistic regression analysis of MRMPP

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Hong Cheng (chenghong@znhospital.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The complete original data reported in this study cannot be deposited in a public repository because these data are confidential medical records. To request access, contact Dr. Hong Cheng (chenghong@znhospital.cn).

This article does not report the original code.

Any additional information required to reanalyze the data reported in this article is available from Dr. Hong Cheng (chenghong@znhospital.cn) upon request.

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AUTHOR CONTRIBUTIONS

Hong Cheng conceived and designed this research, Yun Lu and Wenjing Li collected the clinical data, An-qi Huang and Xuan-xuan Wang retrieved the dataset, Yun Lu and An-qi Huang performed the data analysis, and Hong Cheng verified the results. All authors interpreted the results, provided revision comments concerning the context, and have approved its submission for publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
SPSS	IBM	https://www.ibm.com/cn-zh/spss

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Ethics approval and consent to participate

All participants were of Asian ethnicity. They were all under the age of 18, 425 of whom were male and 402 of whom were female. This study was approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (No. 2023278K, Data S1). Considering its retrospective design and the use of data from discharged patients with their personal information concealed, the requirement for informed consent was waived.

METHOD DETAILS

Study design and data collection

We conducted a retrospective observational study in Zhongnan Hospital of Wuhan University, which is a top three hospital with 100 pediatric beds. Children younger than 18 years old who were diagnosed with MPP and were admitted between January 1, 2023, and December 31, 2023, were included.

Data were collected from the electronic medical record including: gender, age, full-term infant, breastfeeding; clinical characteristics at admission (whether cough, whether fever, pulmonary imaging whether changes); medical history; the total number of drug use, co-detection reported by tNGS, medical costs, as well as the antimicrobial treatments during hospital stay and after discharge.

Study population

Children diagnosed with MPP and with MP detected in tNGS report were considered eligible for this study. Exclusion criteria were listed as follows: congenital heart diseases, kidney or liver dysfunction, cancer, systemic diseases such as hematologic and autoimmune disorders, or any chronic disease that may promote the development of severe pneumonia such as asthma. A total of 825 children met the inclusion criteria. Those carrying strains with A2063G and A2064G mutations of 23S rRNA were classified as the MRMPP group (n = 321), while those detected with wild-type MP genes were classified as the MSMPP group (n = 504).

Definitions

Fever was defined as axillary temperature of 37.5°C or higher. The total fever days refers to the total number of fever days in the course of the illness, including before admission and during hospitalization. "Disease course" in this study refers to the days from the onset of symptoms to discharge, which was calculated as the sum of the onset of symptoms to hospital admission and total hospital stay. "Medical history" mainly includes the history of MP infection and various allergies to food or drugs. "Pulmonary imaging changes" which refers to chest X-ray or computed tomography (CT) showing patchy shadows, ground-glass opacity, mesh shadows, scattered strip shadows, white lung changes, tree-in-bud pattern, consolidation, halo sign and bronchiolitis. "No discharge medication" was defined as no antimicrobial treatments were need after discharge. "Discharge medication" was defined as antimicrobial treatments for MPP after discharge, either continuing with the previous regimen or switching to another.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard error of the mean (SEM), non-normally distributed data were shown as medians with interquartile ranges (IQRs), and categorical variables were recorded as numbers (percentages) which were illustrated in the tables. Qualitative variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using the t-test or non-parametric tests when data presented a nonnormal distribution. Variables with $p < 0.1$ in univariate logistic regression models were included in a multivariate logistic regression model to identify the independent risk factors for MRMPP. The p-values are listed in the tables and explained in the results. Statistical tests were two-sided, with statistical significance set at $p < 0.05$.