

Occurrence and Clinical Features of Septicemia in Children Affected by Pneumonia Caused by *Mycoplasma pneumoniae* in Iraq

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Cite this paper as: Jihad N. Abid Albanwawy, Ayad Jawad Kadhim, Ahmad Abdul Hussien Gburi, Ahmad Younus Hasan, Ammar Malik Dukhin, Ahmed Awad Fattooh, Israa Khudhair Obayes (2024) Occurrence and Clinical Features of Septicemia in Children Affected by Pneumonia Caused by *Mycoplasma pneumoniae* in Iraq. *Frontiers in Health Informatics*, 13 (3), 3271-3279

Abstract

Background: *Mycoplasma pneumoniae* (*Mycoplasma pneumonia*) pneumonia in children can be challenging to treat, and the impact of *Mycoplasma pneumonia* blood infection is unclear. The present study aims to determine the prevalence and clinical characteristics of *Mycoplasma pneumonia* septicemia among pediatric patients.

Methods: Children hospitalized at Alazizya general hospital for *Mycoplasma pneumoniae* pneumonia between October 2021 and June 2023 were included. Healthy controls visiting our outpatient clinic for regular physical examinations were also enrolled. *Mycoplasma pneumonia* was detected by real-time polymerase chain reaction (qPCR) analysis of plasma and peripheral blood mononuclear cell (PBMC) samples.

Results: Seventy-four children with *Mycoplasma pneumoniae* pneumonia and 30 healthy children were included. Among children with *Mycoplasma pneumonia* infection, 41 (55.4%) were positive for *Mycoplasma pneumonia* by qPCR (27 in plasma samples, 10 in PBMC samples, and 4 in both). All healthy controls were negative for *Mycoplasma pneumonia* by qPCR.

Conclusions: The prevalence of *Mycoplasma pneumoniae* septicemia in children with *Mycoplasma pneumonia* pneumonia is moderate. However, detection of *Mycoplasma pneumonia* in blood samples may have limited clinical value for guiding treatment.

Introduction

Pneumonia is classified as a lower respiratory tract disease, affecting various parts of the bronchial system and alveoli, and varies in severity depending on comorbidities and pathogens. They can be broadly categorized

based on the setting of infection, i.e. community or hospital. The former is more common and spreads from person to person via droplet infection. Community-acquired pneumonia (CAP) is currently the fourth leading cause of death worldwide, and its high mortality rate makes it worthwhile to continue to gain insight into the treatment of this disease. (Davis et al., 2023).

Mycoplasma pneumoniae (Mycoplasma pneumonia) is a prevalent pathogen causing respiratory infections in the majority of patients, with pneumonia developing in 3% to 13% of cases (Liu et al., 2021). In children, Mycoplasma pneumonia is a common culprit of community-acquired pneumonia (CAP), accounting for 10% to 40% of CAP cases (Ma et al., 2024; Ogawa et al., 2020). During the current outbreak in China, MPP has commonly been seen in children aged 5 and above. However, compared to previous years, this outbreak has shown a younger age trend in children under 3 years. The principal manifestations of *M. pneumoniae* infection are fever and cough, with moderate-to-high fever being common, but may present as low-grade fever or no fever at all. Some children may experience fever accompanied by symptoms, such as chills, headaches, chest pain, and chest tightness; others may experience wheezing, and in severe cases, shortness of breath and difficulty breathing may occur (Yan et al., 2024). Fortunately, most Mycoplasma pneumonia respiratory infections are self-limiting. Nevertheless, in recent decades, various factors have heightened the complexity of treating Mycoplasma pneumonia pneumonia in children. Examples include rising trends in Mycoplasma pneumonia drug resistance and an increase in the proportion of patients with severe Mycoplasma pneumonia pneumonia.

The majority of research on Mycoplasma pneumoniae infection has predominantly focused on the clinical aspects of Mycoplasma pneumonia pneumonia, with limited knowledge about Mycoplasma pneumonia bloodstream infection. In 1974, Naftalin et al. first isolated Mycoplasma pneumonia strain from the blood, and a recent study by Scapani et al. reported the isolation of another Mycoplasma pneumonia strain from a blood culture. These findings suggest that Mycoplasma pneumonia bloodstream infection is a common occurrence in clinical practice and may contribute to the development of extrapulmonary Mycoplasma pneumonia-associated diseases. In a previous study, Daxboeck et al. identified Mycoplasma pneumonia in the bloodstream of a significant proportion of patients with Mycoplasma pneumonia infection. However, this study solely relied on polymerase chain reaction (PCR) from serum as the diagnostic tool for Mycoplasma pneumonia infection, and alternative techniques and sampling methods may enhance Mycoplasma pneumonia detection. The clinical characteristics of Mycoplasma pneumonia bloodstream infection remain uncertain, emphasizing the need for further investigations.

Beyond causing lung injury, Mycoplasma pneumoniae infection can lead to extrapulmonary manifestations. The prevailing belief is that Mycoplasma pneumonia has the ability to disseminate to other organs through the bloodstream, causing injuries to these organs. This could elucidate why Mycoplasma Pneumonia bloodstream infection is more prevalent in patients with extrapulmonary Mycoplasma pneumonia infection compared to those with pulmonary Mycoplasma pneumonia infection (Dawood et al., 2022). Moreover, distinctive immune responses may be linked to Mycoplasma pneumonia bloodstream infection. As an illustration, a patient with Mycoplasma pneumonia bloodstream infection was reported to have an elevated level of inter-alpha-trypsin inhibitor heavy chain H4 in the serum (Liu et al., 2021).

In recent times, PCR has been employed for the identification of Mycoplasma pneumoniae bloodstream infection. In this investigation, real-time PCR (qPCR) was utilized to detect Mycoplasma pneumonia in plasma and peripheral blood mononuclear cell (PBMC) samples, aiming to assess the prevalence of Mycoplasma pneumonia bloodstream infection in children with Mycoplasma pneumonia pneumonia. Comparative analysis

of the clinical data of children with and without Mycoplasma pneumonia bloodstream infection was conducted to pinpoint any significant differences associated with bloodstream infection.

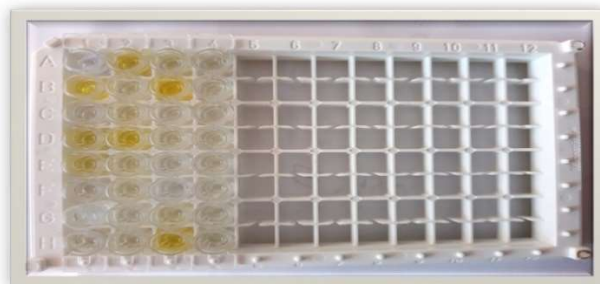
Patients and methods

Patients

Between October 2021 and June 2023, children (aged <13 years) admitted to Alazizya general hospital and hospitalized for Mycoplasma pneumonia pneumonia were included in the study. Healthy controls were selected from individuals visiting our outpatient clinic for regular physical examinations without a reported medical history. Suspected Mycoplasma pneumonia pneumonia was defined by a positive IgM titer (>1:4) or an increase in the IgG titer of >4 times the initial value. The exclusion criteria were chronic respiratory tract infection and macrolide therapy within the previous 2 weeks.

Mycoplasma pneumoniae IgG assay

A serum sample was collected from each patient, and the presence of anti-Mycoplasma pneumoniae (Mycoplasma pneumonia) antibodies in the serum was determined using a passive agglutination assay (Serodia-MYCO II, Fuji Rebio Ltd., Tokyo, Japan) following the manufacturer's instructions. The test was considered positive if a specimen displayed a negative (-ve) result with unsensitized particles (1:20 final dilution) but a positive (+ve) result with sensitized particles (1:40 final dilution). Conversely, the test was deemed negative if a specimen showed a negative (-ve) result with sensitized particles (1:40 final dilution).



Polymerase chain reaction PCR

To detect Mycoplasma pneumoniae in peripheral blood mononuclear cell (PBMC) and plasma samples, the following procedures were employed. For plasma, whole blood samples treated with ethylenediaminetetraacetic acid were collected and centrifuged at 2000 g for 10 minutes. Subsequently, plasma was further centrifuged at 13,500 g for 10 minutes. Following centrifugation, the supernatant was discarded, and the remaining sample was utilized for DNA extraction.

PBMCs were isolated through gradient separation using Ficoll-Histopaque (10771; Sigma-Aldrich, St. Louis, MO, USA). After separation, the cells underwent three washes with phosphate-buffered saline and were then pelleted by centrifugation for DNA extraction.

Quantitative polymerase chain reaction (qPCR) was conducted using a commercial kit designed for Mycoplasma pneumonia DNA (PCR Fluorescence Probing; Daan, Guangzhou, China). It's important to note that the product is specifically intended for use with sputum and throat swab samples and is not recommended for use with blood samples.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means (standard deviations) or medians (25th and 75th percentiles). Categorical variables were presented as frequencies (percentages). Group differences were evaluated using the student’s t-test or Mann–Whitney U test for normally and non-normally distributed continuous variables, respectively. Differences in categorical variables were assessed using Chi-square or Fisher’s exact tests. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

Between October 2021 and June 2023, a total of 74 children (aged <13 years) with Mycoplasma pneumonia pneumonia met the inclusion criteria and were enrolled. The mean (standard deviation) age was 6.20 3.74 years, and 57.4% (n 35) of patients were male. In addition, 30 healthy children with no previous medical history were selected as controls (male, n 23; female, n 7; mean age 4.56 3.82 years). Baseline characteristics did not differ significantly between the two groups. Table 1 and Supplementary Table 1 show the clinical characteristics of pediatric patients Mycoplasma pneumonia pneumonia with and without Mycoplasma pneumonia bloodstream infection.

	MP pneumonia cases (N ¼ 61)					MP qPCR (–) (n ¼ 30)	P (p vs. –)	Total	Healthy controls (n ¼ 30)
	MP qPCR (p) (n ¼ 31)			P	Total				
	Plasma	PBMCs	Both						
N	19 (61.3%)	8 (25.8%)	4 (12.9%)		31 (50.8%)	30		61	30
Sex (male:female)	12:7	4:4	2:2	0.770	18:13	17:13	0.912	35:26 ^b	23:7
Age, years	5.53 3.82	8.78 4.35	8.5 1.29	0.095	6.76 3.97	5.63 3.45	0.244	6.20 3.74 ^b	4.56 3.82
Underlying diseases/symptoms									
Wheeze	7 (36.8%)	2 (25%)	1	0.708	10 (31.25%)	4 (13.3%)	0.079	14	
Laboratory examinations									
Throat swab	5 (22.7%)	2 (9.1%)	3 (13.6%)	0.309	10 (45.5%)	12 (54.5%)	0.601	22	
MP qPCR (p)									
Throat swab	5 (26.3%)	3 (15.8%)	1 (5.3%)		9 (47.4%)	10 (52.6%)		19	
MP qPCR (–)									
LDH, U/L	352.84 73.55 ^a	278.63 89.39	266.75 43.42	0.030	322.58 82.52	353.14 99.56	0.203		

Data are shown as mean standard deviation or n (%).

^a $P < 0.05$ compared with PBMC group or both PBMC and plasma group.

^b $P > 0.05$ compared with healthy control group.

LDH, lactate dehydrogenase; MP, Mycoplasma pneumoniae; PBMC, peripheral blood mononuclear cell; qPCR, real-time polymerase chain reaction; U, units.

Prevalence of Mycoplasma pneumonia bloodstream infection in pediatric patients with Mycoplasma pneumonia pneumonia

The prevalence of Mycoplasma pneumonia bloodstream infection was estimated based on qPCR detection of Mycoplasma pneumonia in PBMC and plasma samples from all patients with Mycoplasma pneumonia pneumonia (n 74). Samples from 41 patients (55.4%) were positive; Mycoplasma pneumonia was detected in the PBMCs of ten patients, in the plasma of 27 cases, and in both the plasma and PBMCs of four patients. All healthy controls were negative for Mycoplasma pneumonia by qPCR analysis of PBMC and plasma samples.

Comparison of clinical characteristics between groups

The clinical characteristics of pediatric patients with Mycoplasma pneumoniae (Mycoplasma pneumonia pneumonia) were compared between those with and without bloodstream infection. Age, sex, fever,

hospitalization time, symptoms, and laboratory tests did not show significant differences between the two groups.

Quantitative polymerase chain reaction (qPCR) was used to detect the presence of *Mycoplasma pneumoniae* in throat swabs for 41 patients, with 22 testing positive. Among children with a positive throat swab for *Mycoplasma pneumoniae*, there was a tendency for positive PCR results in plasma alone (rather than positive results in peripheral blood mononuclear cells (PBMCs) or in both PBMCs and plasma). Additionally, the mean age of children with a positive plasma *Mycoplasma pneumoniae* qPCR result showed a lower trend compared to the mean ages of children with positive results from PBMCs or both PBMCs and plasma.

Wheezing was notably more common in cases of *Mycoplasma pneumoniae* pneumonia with *Mycoplasma pneumoniae* bloodstream infection compared to cases without *Mycoplasma pneumoniae* bloodstream infection ($P < 0.05$). Furthermore, associations between plasma *Mycoplasma pneumoniae* load and clinical characteristics (fever, time between symptom onset and admission, time to fever clearance, hospitalization time, and time from fever onset to discharge) were investigated, revealing no significant differences.

Discussion

This study found that the prevalence of *M. pneumoniae* bloodstream infection in pediatric patients with *M. pneumoniae* pneumonia was 55.4%. Although clinical features associated with bloodstream infection were evaluated, no variables associated with *M. pneumoniae* bloodstream infection were found. Therefore, the clinical value of detecting *M. pneumoniae* bloodstream infection for the treatment of pediatric patients with *M. pneumoniae* pneumonia may be limited.

M. pneumoniae strains have been identified in previous studies by Naftalin et al. and Scapini et al., using culture methods to isolate them from the blood. However, these methods are often unsuccessful in isolating *M. pneumoniae*, which limits their use in *M. pneumoniae*-related diagnostics. This challenge is further exacerbated by the low levels of *M. pneumoniae* in the blood. Fortunately, Narita et al. used PCR to detect *M. pneumoniae* in the blood in 1996. According to their study, the prevalence of *M. pneumoniae* bloodstream infection in pediatric patients with *M. pneumoniae* was very low, only 4% (1/25), which is in sharp contrast to the higher prevalence in this study. This discrepancy may be due to the different methods used in the studies to detect *M. pneumoniae* (PCR vs. qPCR).

recently conducted a study on pneumococcal infections in adults. They investigated the effectiveness of conventional PCR and qPCR for detecting *M. pneumoniae* in blood. They found that PCR gave negative results in all patients ($n = 29$), whereas qPCR gave positive results in 52% of patients ($n = 15$). Interestingly, the qPCR results in this adult population were similar to those in the current pediatric study, suggesting that *M. pneumoniae* bloodstream infection may be more common in *M. pneumoniae* patients than previously thought. Furthermore, healthy controls tested in this study showed negative qPCR results for *M. pneumoniae* in all cases, confirming the absence of *M. pneumoniae* DNA in the blood of children not infected with *M. pneumoniae*.

Among children with *Mycoplasma pneumoniae* (*Mycoplasma pneumoniae*) pneumonia, 41 (55.4%) tested positive for *Mycoplasma pneumoniae* bloodstream infection by quantitative polymerase chain reaction (qPCR), with 27 in plasma, 10 in peripheral blood mononuclear cells (PBMCs), and 4 in both. These results indicate the presence of *Mycoplasma pneumoniae* in both plasma and blood cells. In line with this, in vitro experiments have demonstrated that *Mycoplasma pneumoniae* can adhere to human red blood cells. Recent experiments by Deas *et al.* revealed interactions between *Mycoplasma pneumoniae* and human blood red cells through scanning and

transmission electron microscopy. A proposed mechanism suggests that *Mycoplasma pneumoniae* adheres to red blood cells and subsequently disseminates from the lungs to other sites. While the pathogenesis of *Mycoplasma pneumoniae* infection is generally associated with harmful effects on the host cell epithelium, and intracellular growth and replication of *Mycoplasma pneumoniae* have been described *in vitro*, this process has not been conclusively demonstrated during natural infection. The current findings suggest that *Mycoplasma pneumoniae* could also adhere to PBMCs.

The reasons for the differential detection of *M. pneumoniae* in plasma and peripheral blood mononuclear cells (PBMCs) of patients with *M. pneumoniae* in children are not completely understood. It is not simply due to low DNA content in the samples. One possible explanation is that *M. pneumoniae* adheres to cells early in infection and can initially be detected in PBMC samples by quantitative polymerase chain reaction (qPCR). The pathogen is then released into the bloodstream, where it can be detected in plasma by qPCR. The distribution of *M. pneumoniae* between cells and plasma appears to change as the clinical course of *M. pneumoniae* pneumonia progresses..

Two key points from the study results support this explanation. First, children with a positive qPCR result for *Mycoplasma pneumoniae* in PBMCs had a shorter period between symptom onset and qPCR than those with a positive result for *Mycoplasma pneumoniae* in plasma (7.5 ± 8.16 days vs. 9.84 ± 6.18 days). Second, in some cases, PBMC and plasma qPCR analyses were conducted at different times for the same child (at admission and two weeks after hospitalization). In some children, PBMC qPCR analysis was positive for *Mycoplasma pneumoniae* at admission (but negative in plasma), while two weeks later, plasma qPCR for *Mycoplasma pneumoniae* became positive. Moreover, the prevalence of *Mycoplasma pneumoniae* bloodstream infection was similar in children with a positive throat swab qPCR result and those with a negative result. This finding suggests that the time required for *Mycoplasma pneumoniae* clearance differs between the throat and blood, with *Mycoplasma pneumoniae* appearing in the throat first and then disseminating to the blood. Similarly, after treatment, *Mycoplasma pneumoniae* disappears from the throat first and then from the blood. Although a false-negative result for *Mycoplasma pneumoniae* may occur in qPCR analysis of blood, qPCR remains a valuable tool for evaluating the *Mycoplasma pneumoniae* burden in samples.

symptoms arising from *Mycoplasma pneumoniae* infection extend beyond the lungs. Three potential mechanisms may explain the extrapulmonary manifestations of *Mycoplasma pneumoniae* infection. First, lipoproteins localized at the membrane of *Mycoplasma pneumoniae* could elicit an inflammatory response with cytokine release. Second, immune modulation, including autoimmune responses induced through cross-reactivity between bacterial cell components and human cells, may result in indirect injury. Third, the bacterium may induce vascular occlusion, leading to vasculitis and/or thrombosis, with or without a systemic hypercoagulable state. The blood dissemination of *Mycoplasma pneumoniae* is deemed significant in the pathogenesis of *Mycoplasma pneumoniae* infection based on these mechanisms.

For instance, Stamm *et al.* reported a fatal case of acute disseminated encephalomyelitis following *Mycoplasma pneumoniae* pneumonia, confirmed by subsequent autopsy findings. Prior to the current study, the hypothesis was that children with *Mycoplasma pneumoniae* bloodstream infection would experience more severe infection than those without bloodstream infection. However, no significant differences were found in most clinical characteristics between the two groups, including hospitalization time, fever, underlying diseases, and laboratory results. Children with a positive result of plasma qPCR analysis for *Mycoplasma pneumoniae* were younger than those with positive results from PBMC RT-PCR analysis or both plasma and PBMC qPCR.

Overall, the results indicate that bloodstream infection did not exacerbate *Mycoplasma pneumoniae* infection severity, as observed in the comparison of clinical characteristics between groups. Although the presence of *Mycoplasma pneumoniae* in the blood has been demonstrated in many studies, the clinical impact of the infection remains unclear. Additionally, Narita et al. showed that *Mycoplasma pneumoniae* bloodstream infection is more common in patients with extrapulmonary *Mycoplasma pneumoniae* infection than in those with pulmonary *Mycoplasma pneumoniae* infection. Further analysis is necessary to investigate the mechanism of *Mycoplasma pneumoniae* bloodstream infection and its role in the pathogenesis of extrapulmonary *Mycoplasma pneumoniae* infection.

Conclusions

Mycoplasma pneumoniae bloodstream infection is common in children with *M pneumoniae*, with a moderate prevalence. Interestingly, the clinical characteristics of patients with *M pneumoniae* and *M pneumoniae* bloodstream infection were not significantly different from those of patients with *M pneumoniae* but without bloodstream infection. This suggests that the clinical value of detecting *M pneumoniae* bloodstream infection may be limited in distinguishing the two groups.

However, it is worth noting that more research is needed to explore the characteristics of *M pneumoniae* bloodstream infection. Further research may provide more insight into the impact and potential clinical significance of *M pneumoniae* in the blood and help improve the recognition and treatment of *M pneumoniae* infection in children.

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