

# *Mycoplasma pneumoniae* Infection in Children

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## ABSTRACT

*Mycoplasma pneumoniae* is an important cause of community-acquired pneumonia in school-aged children and adults and the incidence is also increasing in other age groups. It has a varied presentation and apart from respiratory system involvement, it also involves many other systems of the body. In children, central nervous system involvement is very common followed by dermatological, hematological, and other systems. Extrapulmonary manifestations can even cause long-term sequel. Since this organism does not have a cell wall, the diagnosis is always difficult and a strong possibility has to be kept in mind so that the treatment can be started early. The choice of antibiotics is limited, as beta-lactam antibiotics (which act on the cell wall) do not act on it. In this article, we have reviewed the up-to-date knowledge of *M. pneumoniae* infection in children.

**Keywords:** Atypical pneumonia, Community-acquired pneumonia, Extrapulmonary manifestations, *Mycoplasma pneumoniae*.

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## HISTORY AND INTRODUCTION

As early in 1898, Nocard and Roux first isolated an agent that was assumed to be the cause of cattle pneumonia and was named as "microbe de la peripneumonie."<sup>1-6</sup> Microorganisms from other sources were also found to have properties similar to this pleuropneumonia organism (PPO) of cattle, which was known as pleuropneumonia-like organisms (PPLOs), but their true nature was not known.<sup>4-6</sup> Many PPLO were later proven to be the cause of pneumonia and arthritis in several lower animals.<sup>4,7,8</sup> In 1930s in the United States, some patients were diagnosed with pneumonia but there symptoms were found to be different from that of bacterial pneumonia or influenza-like viruses. For many years, this organism was known as filterable virus that could pass through the Seitz filter and was recognized as psittacosis-like or a new virus. Later in 1944, Monroe Eaton used embryonated chicken eggs to cultivate an agent thought to be the cause of human primary atypical pneumonia (PAP), commonly known as "walking pneumonia."<sup>9</sup> It is known as walking pneumonia because of its benign nature specially early in the course of disease.

## EPIDEMIOLOGY

Pneumonia is the most common presentation of *Mycoplasma*. Its incidence is more common in school-aged children and adults but it causes infection in all age groups. The geographic presentation of *Mycoplasma* infection is also varied, involving almost all the countries.<sup>10</sup> The exact incidence of *Mycoplasma pneumoniae* infections remains underdiagnosed because of its presumed benign nature, lack of diagnostic tests with good sensitivity and specificity, and its clinical presentations mimic with other infections also. The incidence is found to be higher in patients who are suffering from asthma and other chronic lung conditions. There have been recent outbreaks in children and adults according to the Centers of Disease Control and Prevention (CDC).<sup>11</sup> Pneumonia due to *M. pneumoniae* increases with age (2% in children <2 years, 5% in age group 2-4 years, 16% in the age group 5-9 years, and 23% in the age group 10-17 years).<sup>12</sup>

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## PATHOGENESIS

There are five genera (*Mycoplasma*, *Ureaplasma*, *Acholeplasma*, *Anaeroplasm*, *Asteroloplasma*) in the class Mollicutes and the term *Mycoplasma* is used for any of these organisms.<sup>2</sup> *Mycoplasma pneumoniae* is the fastidious organism that lack the cell wall, though it can be grown under both anaerobic and aerobic conditions and also can be isolated on the media supplemented with serum. *Mycoplasma pneumoniae* is divided into two genetic groups, subtype 1 and subtype 2. *Mycoplasma pneumoniae* infection is likely a consequence of the interplay between the two subtypes, each emerging after the other induces transient herd immunity.<sup>13</sup> The most important intrinsic virulence factors include cytoadherence and mobility. The main anchor proteins P1 and P30 are attached to the polar terminal organelle of the pathogen, which help in adherence of the organism. The infection is associated with elevated mRNA levels of cytokines, including interleukin (IL)-8, tumor necrosis factor- $\alpha$ , and IL-1 $\beta$ , which lead to the recruitment of the inflammatory cell.<sup>10,14</sup>

The mechanism of infection include:

- Direct infection with the organism at the site of inflammation and activation of local cytokines.
- Indirect infection by modulating the immune system that may involve cross-reactivity between bacterial and human cells. These include cold agglutinins to I-antigen of human red blood cells.<sup>15</sup>
- Vasculitis and/or thrombosis.<sup>16</sup>

## CLINICAL MANIFESTATIONS

The symptoms of *M. pneumoniae* infection in children can be varied. It can be just an asymptomatic carrier or it can cause mild respiratory symptoms like cold and cough or can involve lower respiratory infections like pneumonia, asthma-like symptoms, and leading to more serious manifestations involving the other systems of the body. The clinical profile of *M. pneumoniae* infections is discussed further in Table 1.

**Table 1:** Pulmonary and extrapulmonary manifestations of *M. pneumoniae* infection<sup>1-3</sup>

Organ involvement	Manifestations
Pulmonary	<ol style="list-style-type: none"> <li>1. Asthma</li> <li>2. Chronic obstructive pulmonary disease (COPD) exacerbation</li> <li>3. Tracheobronchitis</li> <li>4. Pneumonia: lobar and multilobar infiltrates</li> <li>5. Diffuse alveolar hemorrhage</li> </ol>
Gastrointestinal	<ol style="list-style-type: none"> <li>1. Nausea and vomiting</li> <li>2. Abdominal pain, anorexia</li> <li>3. Diarrhea</li> <li>4. Raised liver enzymes</li> </ol>
Cardiovascular	<ol style="list-style-type: none"> <li>1. Myocarditis, pericarditis</li> <li>2. Cardiac arrhythmias</li> <li>3. Thrombotic events</li> </ol>
Neurological	<ol style="list-style-type: none"> <li>1. Meningitis</li> <li>2. Encephalitis</li> <li>3. Optic neuritis</li> <li>4. Guillain-Barre syndrome</li> <li>5. Acute disseminated encephalomyelitis (ADEM)</li> <li>6. Transverse myelitis</li> <li>7. Cerebellar ataxia</li> <li>8. Cranial nerve palsies</li> </ol>
Renal	<ol style="list-style-type: none"> <li>1. Acute tubular necrosis</li> <li>2. Glomerulonephritis</li> <li>3. Interstitial nephritis</li> </ol>
Musculoskeletal and skin	<ol style="list-style-type: none"> <li>1. Erythema nodosum, cutaneous leukocytoclastic vasculitis</li> <li>2. Erythema multiforme, SJS</li> <li>3. <i>Mycoplasma pneumoniae</i>-associated mucositis</li> <li>4. Myopathy, arthritis, and rhabdomyolysis</li> </ol>
Thrombotic	<ol style="list-style-type: none"> <li>1. Pulmonary embolism</li> <li>2. Splenic artery and left atrium and right ventricle thrombosis</li> <li>3. Aortic thrombosis/renal artery thrombosis</li> </ol>
Hematological	<ol style="list-style-type: none"> <li>1. Cytopenias</li> <li>2. Cold agglutinin-induced autoimmune hemolytic anemia</li> <li>3. Sickle cell anemia</li> <li>4. Idiopathic thrombocytopenic purpura-like syndrome</li> </ol>
Others	<ol style="list-style-type: none"> <li>1. Vasculitis (positive antineutrophil cytoplasmic antibodies)</li> <li>2. Kawasaki disease</li> </ol>

Respiratory system involvement is the most common manifestation of *M. pneumoniae* infection in children. Most of them have mild upper respiratory symptoms, which are usually self-limiting. Its onset is gradual starting with cough, fever, headache, malaise, sore throat, leading to breathing difficulty and gradually involving other systems of the body. Cough is the important manifestation; it can be dry or productive because of tracheobronchitis and can even persist for days to weeks. Community-acquired pneumonia is the common presentation in school-aged children. The person remains in the carrier state for a time much longer than symptoms and it does not change by the antibiotic therapy.

Neurological manifestations are the next common in children. The incubation period for the development of central nervous system (CNS) symptoms after the respiratory symptoms manifest varies from 2 to 23 days (mean 10 days), but in about 5% of patients there may not be any preceding respiratory symptoms. Encephalitis within 5 days of the prodromal symptoms may be because of the direct invasion of the organism in the brain. Encephalitis after 7 days of prodromal symptoms may be because of the autoimmune response and is more common than the direct infection. Other CNS manifestations are described in the Table 1.

Dermatological manifestations may range from simple maculopapular rash to bullous papular purpuric gloves and socks syndrome, urticaria rash, and in some children more severe manifestations like Steven Johnson syndrome (SJS). Some studies have proved that the cause of SJS may be the direct invasion of bacteria in skin. Other skin manifestations like urticaria, anaphylactoid purpura, and erythema multiforme are most likely immunologically mediated.

Hematological system involvement in the form of hemolysis can occur due to the cold agglutinin response due to appearance of IgM antibodies against I antigen on the erythrocyte membrane. This may be clinically insignificant in normal patients but can be severe in patients with underlying diseases like sickle cell anemia.

The other important extrapulmonary manifestations are discussed in Table 1. In children with community-acquired pneumonia and multisystem involvement, *M. pneumoniae* should always be considered.

## DIAGNOSIS

Since *M. pneumoniae* is without cell wall, diagnosing it is always a challenge.

In community-acquired pneumonia, X-ray chest is always done for confirmation, though in 5% of patients with *M. pneumoniae* pneumonia, X-ray chest may be normal. Common patterns in chest X-ray of *M. pneumoniae* patients are the following:

- Peribronchial and perivascular interstitial infiltrates (49%)
- Airspace consolidation (38%)
- Reticulonodular opacification (8%)
- Nodular or mass-like opacification (5%)

Other findings include pleural effusion, cavitory disease, and hilar lymphadenopathy.<sup>1</sup>

Total leucocyte count and inflammatory markers like C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) may be elevated but they do not differentiate it from other causes of pneumonia and are not helpful. In patients with CNS involvement, cerebrospinal fluid (CSF) shows lymphocytic pleocytosis, elevated protein, and normal glucose.<sup>2</sup>

There is no single confirmatory test for *M. pneumoniae* infection. Cultures on special media (SP4 agar media) of the sputum sample may show classical mulberry colonies but it requires the incubation period of 7–21 days and is not done routinely in most of the laboratories.

Antigen detection can be done by antigen capturing EIA (AgEIA), which may detect  $10^4$  colony-forming units/mL. The disadvantage of using this is that the ability to detect the antigen may vary with time of sampling and it has been largely replaced by molecular testing. The best method of diagnosis is the combination of the nucleic acid amplification test (NAAT) including the PCR-based assay and the serology.<sup>2,10</sup> The PCR of the nasopharyngeal and throat swab for *M. pneumoniae* DNA has a sensitivity and specificity of 80 and >97%. The PCR is more reliable in the acutely ill patients and the infection becomes undetectable by PCR once the antibiotic therapy is started.

Fourfold increase in antibiotic titers remains the gold standard for diagnosis (IgM antibody titers rise earlier than IgG). Both PCR and serology may not be concordant in elderly and infants due to an insufficient immunological response toward the infection.

Cross-reacting antibodies against red blood cells called cold agglutinin titer may be raised in patients with *M. pneumoniae* infection by 2nd week of illness and resolves by 6–8 weeks. In a child with pneumonia, titers more than 1:64 can be due to *M. pneumoniae*, but has low specificity. There is also cross-reactivity with Epstein-Barr virus (EBV).<sup>17</sup> Cold agglutinins may be elevated in 50–60% of *Mycoplasma pneumoniae* pneumonia (MPP) patients but can also be present in EBV, cytomegalovirus, or *Klebsiella* infections.

Other modern diagnostic techniques that lack widespread validity include nanorod array-surface-enhanced Raman spectroscopy (NA-SERS) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS).<sup>10</sup>

Important points in *M. pneumoniae* in children:

1. Incidence of *M. pneumoniae* infection in children of all age groups is increasing.
2. *Mycoplasma pneumoniae* has no cell wall.
3. Clinical symptoms can be asymptomatic carrier, community-acquired pneumonia, CNS, and other extrapulmonary manifestations.
4. Diagnosis is difficult; combination of PCR and serology is the best method of diagnosis.
5. Treatment is with macrolides, tetracycline, and fluoroquinolones.
6. There is no vaccine available; main prevention is by stopping the droplet spread.

## TREATMENT

*Mycoplasma pneumoniae* infection resolves on its own in 7–10 days but treatment is often necessary. Since *M. pneumoniae* is without the cell wall, the choice of antibiotics is also limited as beta-lactam antibiotics that act on the cell walls do not act on it and hence the antibiotics that act on the ribosome remain the choice of treatment. Since the diagnosis is difficult early in the disease, empiric antibiotics are usually started. The choice of antibiotics include macrolides, ketolides, streptogramins, and tetracyclines. Macrolides are bacteriostatic and have immunomodulatory action. Macrolides and ketolides bind to specific nucleotides of the 23S rRNA in the 50S bacterial ribosomal subunit, blocking protein synthesis by causing

premature dissociation of peptidyl-tRNA from the ribosome.<sup>10,18</sup> Azithromycin has long half-life and has better tolerance and hence remains the drug of choice.<sup>2</sup>

Dose of azithromycin is 10 mg/kg on day 1 orally or intravenously (max 500 mg), followed by 5 mg/kg on day 2 to day 5 (max 250 mg).

Dose of clarithromycin is 15 mg/kg per day in two divided doses for 10 days (max 1 g).

The other drugs like tetracycline can be used in children more than 8 years of age. The dose of doxycycline is 2–4 mg/kg orally or intravenously in one to two divided doses for 10 days (max 200 mg per day).

There has been widespread resistant to macrolides called macrolide-resistant *M. pneumoniae* (MRMP), which was first seen in Japan and later seen in many other countries. In a study done in 8 hospitals of United States during 2015–2018, macrolide resistance was seen in 7.5% of total patients.<sup>19</sup> As an alternative, fluoroquinolones have been used as second-line treatment in immunocompetent children and an alternative in immunocompromised patients specially if they have macrolide exposure before.

Dose of levofloxacin is for children >5 years of age, 10 mg/kg per dose (max 750 mg per day) once a day orally or intravenously for 10 days.

For children 6 month to 5 years, the dose is 8–10 mg/kg per dose in two divided doses orally or intravenously (max 750 mg per day) for 10 days.

Extrapulmonary manifestations may need adjunctive treatment. Steroids, diuretics, and immunotherapy (intravenous immunoglobulin and plasmapheresis) can be used in patients with severe life-threatening conditions with CNS, hematological involvement, and dermatological conditions like SJS.<sup>3</sup>

## PREVENTION

In hospitalized patients, precautions should be taken to prevent the spread through respiratory droplets. *Mycoplasma pneumoniae* remains contagious for a long time even after the antibiotic therapy, which should be explained to the patients. There have been many vaccine trials for *M. pneumoniae* but none has been successful and there is no vaccine at present for the prevention. There is no role of giving prophylactic antibiotics to the contacts, though can be considered in household contact with high-risk patients like sickle cell anemia.<sup>2,3</sup>

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