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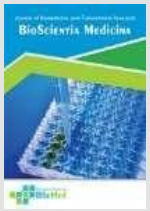

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Mycoplasma pneumoniae Infection: An Updated Narrative Review

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A B S T R A C T

Pneumonia cases in China, which rose sharply from October to November 2023, have received particular attention in the world of health. Chinese authorities said the trigger was not a new pathogen, one of which was *Mycoplasma. Mycoplasma pneumoniae* is a bacteria that can cause disease by damaging the lining of the respiratory system. *Mycoplasma pneumoniae* infection can occur in all age groups, especially at school and pre-school age. Most studies report that the age group that most often experiences *Mycoplasma pneumoniae* infection is those aged over 5 years. The importance of recognizing symptoms and providing adequate therapy is very necessary to treat pneumonia caused by *Mycoplasma pneumoniae* infection.

1. Introduction

Pneumonia cases in China, which rose sharply from October to November 2023, have received particular attention in the world of health. The surge in pneumonia cases affecting many children has caused health facilities in China to become overloaded. However, the World Health Organization (WHO) and Chinese authorities say the trigger is not a new pathogen, one of which is *Mycoplasma. Mycoplasma pneumoniae* is a bacteria that can cause disease by damaging the lining of the respiratory system.[1]

Mycoplasma pneumoniae is thought to be associated with chronic lung disease and bronchial asthma. Apart from being associated with respiratory tract diseases, *Mycoplasma pneumoniae* is also thought to cause extrapulmonary complications in the skin, kidneys, stomach, intestines, heart, musculoskeletal, brain, and circulatory systems. Extrapulmonary clinical manifestations often occur without pneumonia, and both involve different pathological mechanisms.[2,3] *Mycoplasma pneumoniae* infection can occur in all age groups, especially at school and pre-school age. Most studies report that the age group most often experiences Mycoplasma pneumoniae infection in those over five years. Defilippi et al. reported that the rate of *Mycoplasma pneumoniae* infection in school-aged children reached 41.75%.[4-6]

The increasing trend in *Mycoplasma pneumoniae* infections is likely due to increased drug-resistant strains. Excessive and inappropriate use of antibiotics can cause an increase in the number of resistant strains, causing severe clinical symptoms and making treatment more difficult. Recognizing symptoms and providing adequate therapy are necessary to treat pneumonia caused by *Mycoplasma pneumoniae* infection. Hopefully, this review article can provide a

narrative approach to cases of *Mycoplasma pneumoniae* pneumonia.

Mycoplasma pneumoniae

Mycoplasma pneumonia is a significant cause of respiratory tract infections in children and adults, with severity ranging from mild to life-threatening.[2] *Mycoplasma pneumoniae* is a cause of community-acquired respiratory tract infections in both children and adults. *Mycoplasma pneumoniae* does not have a cell wall, so it is not susceptible to antibiotics that interfere with cell wall synthesis, such as beta-lactams.[3-4] Antibiotics effective against *Mycoplasma pneumoniae* include macrolides, tetracyclines, and fluoroquinolones. Macrolides are widely used worldwide, causing alarming levels of resistance to Streptococcus pneumoniae and *Mycoplasma pneumoniae*. Reports of macrolide-resistant *Mycoplasma pneumoniae* (MR-MP) prevalence are very high in Asia, reaching more than 90% in some areas, making *Mycoplasma pneumoniae* challenging to cure.[5]

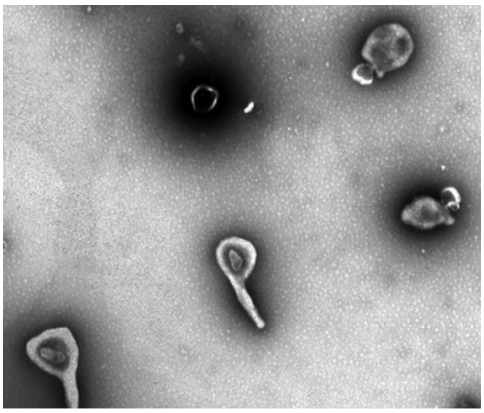

Figure 1. Image of *Mycoplasma pneumoniae* on an electron microscope.[2]

Epidemiology

Mycoplasma pneumoniae infection is one of the primary pathogens causing community-acquired pneumonia in children. Research conducted in Suzhou province, South China, reported that the prevalence of *Mycoplasma pneumoniae* infection ranged from 30-36.08%. Another study conducted in northern China showed that the rate of *Mycoplasma pneumoniae* infection reached 37.5% in children with pneumonia. Li et al. reported data from hospitals from 2006-2016 in northern China showing an increase in *Mycoplasma pneumoniae* infections; even from June 2013 to May 2014, this infection reached 51.5% of children with pneumonia.[6] Multicenter research conducted by Guo et al. in 2018 in Beijing, China, reported that of 822 tracheal swab specimens collected from children suffering from respiratory tract infections, 41.48% of them (341 samples) were positive for *Mycoplasma pneumoniae* as proven by PCR. Previous research conducted in Beijing reported that the prevalence of *Mycoplasma pneumoniae* infection ranged from 19.13% to 29.07%, so we can conclude that there is an increasing trend in *Mycoplasma pneumoniae* infection.[7]

Mycoplasma pneumoniae infection can occur in all age groups, especially at school and pre-school age. Most studies report that the age group most often experiences *Mycoplasma pneumoniae* infection in those over five years. Defilippi et al. reported that the rate of *Mycoplasma pneumoniae* infection in school-aged children reached 41.75%.[6] Research conducted by Li et al. stated that the prevalence of infection *Mycoplasma pneumoniae* is higher in girls than boys in northern China. It may be because women are more susceptible to *Mycoplasma pneumoniae* infection. However, other studies state that gender is unimportant in *Mycoplasma pneumoniae* infection.[6]

The increasing trend in *Mycoplasma pneumoniae* infections is likely due to increased drug-resistant strains. Excessive and inappropriate use of antibiotics can cause an increase in the number of resistant strains, causing severe clinical symptoms and making treatment more difficult. The emergence of macrolide-resistant *Mycoplasma pneumoniae* (MR-MP) strains is a public health problem that has become a global threat, especially in Asia. The prevalence of antibiotic resistance, especially macrolide, differs in each region. Research conducted by Ishiguro et al. reported that the prevalence of macrolide resistance in Hokkaido varies significantly, from 0% to 100%. Other research states that more than 90% of strains that cause *Mycoplasma pneumoniae* infections in China are caused by resistant strains.[6] Compared with Asia, the spread of MR-MP in Europe is relatively low. The highest prevalence was reported in Italy and Scotland during the 2010–2011 epidemic, whereas in the Netherlands and Finland, there have been no reports of MR-MP infections. The level of *Mycoplasma pneumoniae* resistance can be influenced by the patient's background and the epidemiological situation in each country. The low prevalence of MR-MP in Europe is probably due to the cautious use of macrolides.[7,8]

Pathogenesis

Mycoplasma pneumoniae is thought to be associated with chronic lung disease and bronchial asthma. Apart from being associated with respiratory tract diseases, *Mycoplasma pneumoniae* is also thought to cause extrapulmonary complications in the skin, kidneys, stomach, intestines, heart, musculoskeletal, brain, and circulatory systems. Extrapulmonary clinical manifestations often occur without pneumonia, and both involve different pathological mechanisms.[3]

Mechanism of intrapulmonary infection

In the early stages, *M. pneumoniae* attaches to the host bronchial epithelium via terminal structures, inducing intracellular metabolism and ultrastructural changes in infected cells. At the same time, *M. pneumoniae* also takes nutrients (nutrient depletion) and releases CARDS toxins, hydrogen peroxide, and superoxide radicals, which then cause direct damage. Apart from direct damage mechanisms, *M. pneumoniae* can also cause the release of enzymes, lipids, lipoproteins, glycolipids, and other components that induce cytokine production, resulting in inflammation, which ultimately causes indirect damage. In addition, *Mycoplasma pneumoniae* can cause disturbances in the host's innate and adaptive immunity so that it can help it survive in the body for a long time.[3]

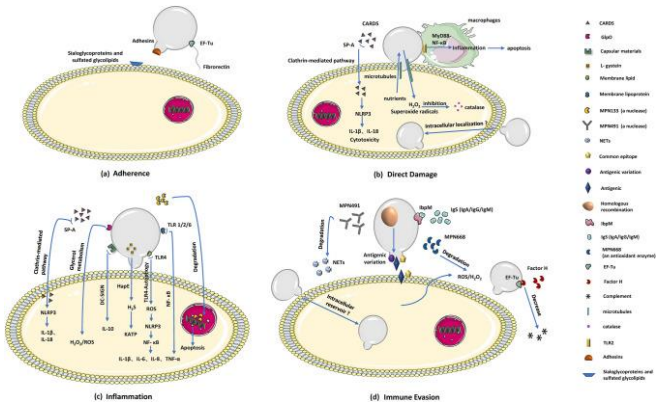

Figure 2. Mechanism of intrapulmonary pathogenesis by *Mycoplasma pneumoniae*.[3]

Adhesions caused by *Mycoplasma pneumoniae* cause cell damage. This adhesion is associated with sialoglycoproteins and sulfated glycolipids receptors on the surface of host cells to obtain nutrients. *M. pneumoniae* then releases CARD toxins, H_2O_2, and superoxide radicals into host cells to cause host cytotoxicity. Then, factors that induce inflammation (membrane lipids, lipoproteins, HapE enzyme, nuclease, GlpO oxidase, capsular materials) activate the host inflammatory pathway, which causes damage. *Mycoplasma pneumoniae* produces nucleases and antioxidant enzymes to degrade NETs and peroxides. This homologous DNA recombination causes antigenic variations, then IbpM and EF-Tu are activated by *Mycoplasma pneumoniae* to evade the host's immune response.[3]

Mechanisms of extrapulmonary infection

Extrapulmonary manifestations caused by *Mycoplasma pneumoniae* can be explained by direct damage caused by invasion or locally induced inflammatory cytokines, indirect immune-mediated damage, and vascular occlusion caused by vasculitis or thrombosis.[3] *Mycoplasma pneumoniae* can cause direct damage to host cells through direct invasion and damage due to inflammation caused by the cytokines produced. Apart from that, *Mycoplasma pneumoniae* can also imitate host cell components and cause changes in the structure of the host cell membrane, thereby stimulating autoimmunity in the host. *Mycoplasma pneumoniae* can also affect blood vessel walls by causing vasculitis and blood vessel occlusion in the form of thrombosis through complement mediators and fibrin D-dimer.[3]

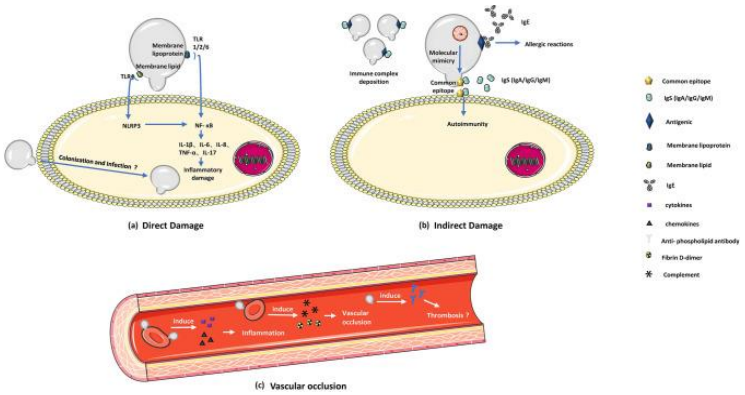

Figure 3. Mechanism of extrapulmonary pathogenesis by *Mycoplasma pneumoniae*.[3]

Risk factors

Factors associated with the risk of *Mycoplasma pneumoniae* infection are still debated. Several studies report risk factors related to *Mycoplasma pneumoniae* infection. Research conducted by Nantanda et al. in 2021 in Uganda analyzed the risk factors for *Mycoplasma pneumoniae* infection in children aged two months to 12 years who experienced coughing and/or difficulty breathing. Nantanda et al. reported a significant relationship between age, female gender, and prematurity. This study found that children aged 12-59 months had a significantly higher risk of experiencing *Mycoplasma pneumoniae*. It is not clear why women are more likely to suffer from *Mycoplasma pneumoniae*. In general, premature children have a greater risk of developing pneumonia, but it is not clear whether prematurity is associated with an increased risk of *Mycoplasma pneumoniae* infection.[9] Another study by Qiu et al. in China reported no significant differences between gender, age, length of time before macrolide administration, white blood cell count (WBC), fibrinogen, activated partial prothrombin time (APTT), Prothrombin time (PT) between *Mycoplasma* severe pneumonia with mild *Mycoplasma* pneumonia.[10]

Diagnosis

Signs and symptoms

The clinical presentation of *Mycoplasma pneumoniae* infection varies greatly. The most common manifestation is tracheobronchitis, with a cough that may be dry or productive with the production of mucoid or mucopurulent sputum. Many patients may have nonspecific symptoms similar to upper respiratory tract infections, such as headache, sore throat, runny nose, and otitis media. Chest auscultation may reveal coarse rales and crackles if the disease is limited to tracheobronchitis, fine rales, and dullness at the base of the lungs if pneumonia occurs.[2] The incubation time for this disease is around 23 days, with common symptoms in the form of a prolonged cough that lasts 3 to 4 weeks in children and adolescents and an average of 54 days in adults.[2]

Laboratory examination

Laboratory examinations in patients with mild *Mycoplasma pneumoniae* infections are usually non-diagnostic in the form of complete blood tests, electrolytes, liver function, and kidney function within normal limits. However, there may be a slight increase in C-reactive protein (CRP). In patients with more severe symptoms, especially primary atypical pneumonia, inflammatory markers (CRP and erythrocyte sedimentation rate).[2]

Imaging

Radiographically, *Mycoplasma pneumoniae* infections may be indistinguishable from viral lower respiratory tract infections, with patchy airspace consolidation and ɣround glass opacities. Abnormalities of radiological findings are usually in the lower lobes. Unilateral pleural effusion often occurs in children. On a chest CT scan, bronchial wall thickening, centrilobular nodules, lymphadenopathy, ground-glass attenuation, and reticular or linear opacity can be found.[2]

Diagnostic test

Mycoplasma pneumoniae infection can be detected using culture, serology, or molecular-based methods. One of the reasons why the detection of *Mycoplasma pneumoniae* is not recommended by many laboratories in the United States is that culture methods are impractical due to their slow growth and require meticulous cultivation requirements. These serological tests require acute-phase and convalescent-phase sera collected at least two weeks apart for results. [2]

The FDA approves no rapid tests for direct detection of *Mycoplasma pneumoniae*. However, some qualitative serologic tests with a moderate complexity classification under the Clinical Laboratory Improvement Amendments can be performed in ambulatory care clinics, with results available within minutes. Tests like this are used often, although single measurements of IgM and/or IgM/IgG are unreliable, especially for adults.[2]

Another reason diagnostic testing is infrequent is that many clinicians do not feel it is necessary to have microbiological confirmation for patient management purposes. This opinion is reflected in clinical practice guidelines for treating community-acquired pneumonia (CAP) that do not recommend pathogen-specific testing.[2]

Therapy

Mycoplasma pneumoniae infection, in most cases, is self-limiting, but complications can occur if the antimicrobial agents are ineffective. Clinical manifestations such as persistent fever and/or more severe clinical symptoms and even extrapulmonary clinical manifestations can occur due to delays in treatment. Early detection and appropriate treatment are essential to prevent damage. Empiric antibiotics commonly used for community-acquired pneumonia, such as beta-lactams, are ineffective in *Mycoplasma pneumoniae* infections because they do not have cell walls. The main drugs used for *Mycoplasma pneumoniae* infection are macrolides, tetracyclines and fluoroquinolones.[11]

First-line antibiotics

In treating *Mycoplasma pneumoniae* infection, macrolides have direct antimicrobial activity, inhibiting protein synthesis and binding to bacterial ribosomes. Apart from that, macrolides also have anti-inflammatory effects on cytokine production, including interleukin-8 (IL-8). Macrolides are the most effective antibiotics against macrolide-sensitive *Mycoplasma pneumoniae*. Therefore, macrolides are recommended as a first-line choice for pneumonia patients with *Mycoplasma pneumoniae* infection who have not received appropriate antibiotics.[11]

The recommended duration of macrolide treatment for *Mycoplasma pneumoniae* infection is 14 days for erythromycin (25-50 mg/kg/day divided into 4-6 doses per day, oral), 10 days for clarithromycin (10-15 mg/kg/day, 2-3 doses/day, oral), and three days for azithromycin (10 mg/kg/day, once daily, oral). The most common side effects after macrolide treatment are gastrointestinal disorders, and azithromycin has the lowest side effect rate and the most prolonged half-life. The response to macrolides can be assessed based on whether or not a decrease in body temperature occurs within 72 hours after starting treatment. If fever persists or clinically does not improve after 72 hours after starting macrolide treatment, the clinician should first rule out other possible causes of pneumonia and administer second-line antibiotics.[11]

Second-line antibiotics

The use of tetracyclines and fluoroquinolones is considered for patients with *Mycoplasma pneumoniae* infection who do not respond to macrolides. Previous research showed that fever subsided within 72 hours after switching to tetracycline or fluoroquinolone in almost all patients with pneumonia due to macrolide-resistant *Mycoplasma pneumoniae* infection. Although tetracyclines and fluoroquinolones are not usually recommended for children, they are the only practical options against macrolide-resistant strains until new drugs are discovered.[11]

Tetracycline inhibits bacterial protein synthesis reversibly by binding to the ribosomal complex. Use in children under eight years is contraindicated because it can cause permanent discoloration of the teeth. Doxycycline has not been proven to cause permanent discoloration of teeth at the recommended dosage and duration of treatment. The recommended dose of doxycycline is 4mg/kg/day divided into two daily doses.[11]

Fluoroquinolones work by inhibiting DNA replication; use in children under 18 years is relatively contraindicated due to cartilage damage in adolescents. Even though it is not as effective as other fluoroquinolone drugs, such as moxifloxacin and levofloxacin, ciprofloxacin has the lowest cartilage toxicity effect among other fluoroquinolone drugs.[11]

Prognosis

Research conducted by Zhao et al. reported that age and the number of polymorphonuclear neutrophils (PMNs) were associated with pneumonia due to refractory *Mycoplasma pneumoniae* (RMPP) infection. Older age was reported to be associated with PMN activation function stimulated by *Mycoplasma pneumoniae*. PMN is said to trigger the release of superoxide and myeloperoxidase (MPO).[12]

Yang et al. examined the difference in prognosis between necrotizing pneumonia caused by *Mycoplasma pneumoniae* (MPNP) and non-*Mycoplasma pneumoniae* (N-MPNP). Yang et al. reported that the prognosis of MPNP was better than that of N-MPNP. Common sequelae of MPNP include pleural thickening, pulmonary fibrosis, and bronchiectasis.[13]

2. Conclusion

Mycoplasma pneumonia is an essential cause of respiratory tract infections in children and adults, with severity ranging from mild to life-threatening. *Mycoplasma pneumoniae* is a cause of community-acquired respiratory tract infections in both children and adults.

Empiric antibiotics commonly used for community-acquired pneumonia, such as beta-lactams, are ineffective in *Mycoplasma pneumoniae* infections

because they do not have cell walls. The main drugs used for *Mycoplasma pneumoniae* infection are macrolides, tetracyclines, and fluoroquinolones. Recognizing symptoms and providing adequate therapy are necessary to treat pneumonia caused by *Mycoplasma pneumoniae* infection.

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