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Review Article

THE PATHOGENIC MECHANISM AND TREATMENT PROGRESS OF MYCOPLASMA PNEUMONIAE PNEUMONIA IN CHILDREN

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ABSTRACT

Mycoplasma pneumoniae Pneumonia (MPP) is one of the important pathogens of a common community-acquired pneumonia (CAP) in children. With the use of macrolide antibiotics, more and more drug-resistant bacteria have emerged, and under the influence of factors such as disorder, mixed infection, and blood hypercoagulability, severe M.pneumoniae pneumonia (SMPP) in children has increased year by year. Refractory MPP, SMPP, and damage to various extrapulmonary systems caused by M. pneumoniae infection have attracted more and more attention from pediatricians. SMPP in children is severe, progresses quickly, and requires a long course of treatment. It is more common in older children. It is often complicated by multiple complications, and severe cases can be life-threatening. So far, the pathogenesis of SMPP has not been fully understood, and there is no unified standard for treatment. Six of the 16 mycoplasma species that infect human are pathogenic, with M. pneumoniae being the one with the most clinical importance[1]. The biological characteristics of M. pneumoniae include population characteristics, genotype, and antimicrobial susceptibility. Through comparative genomics and phylogenetic analyses, it has been suggested that mycoplasma may have originated from Gram-positive Bacteria [2].

Keywords: *Mycoplasma pneumoniae; Pneumonia; severe Mycoplasma pneumoniae pneumonia*

Pathological manifestations of Mycoplasma pneumoniae pneumonia:

Identifying microbial mechanisms and understanding the complex pathophysiology of pneumonia is key to reducing antibiotic overuse and resistance[3]. Excessive inflammation is the pathophysiological basis of M. pneumoniae-induced respiratory tract infection in children. The most typical pathological feature of pneumonia is massive lymphocytic infiltration in the peribronchovascular area, with accumulation of macrophages, neutrophils, and lymphocytes in the alveoli. The presence of plasma cells in the peri bronchial vessels may reflect the expression of humoral immunity induced by M.pneumoniae infection. Studies have demonstrated varying levels of monocytes, macrophages, lymphocytes, eosinophils, and total cell counts, with macrophage and lymphocyte counts increasing more than other cell types. M. pneumoniae infection accelerates Toll-like receptor 2 expression in bronchial epithelial cells and alveolar macrophages[4]. Results from animal models suggested that for persistent inflammation in the lungs, a strong M.Pneumoniae antigen is required to stimulate a host immune response leading to plasma cell infiltration into the peribronchial area.

Pathogenic mechanism of Mycoplasma pneumonia:

Following infection by mycoplasma, the resources of the host cell are utilised for metabolism, survival, and reproduction. M. pneumoniae can adhere to host cell membranes through terminal tip structures (cell-adhesive organelles), which may help it evade immune responses, and can eventually penetrate into cells and exert cytotoxic effects in host cells. Cell adhesion is a prerequisite for pathogenesis, causing ciliary degeneration and affecting glucose metabolism, amino acid uptake, and protein synthesis.

In addition, oxygen free radicals produced by Mycoplasma pneumoniae infection of host cells can cause cell damage and structural changes. Two possible mechanisms for causing MPP are summarised: 1. M. pneumoniae causes direct damage to respiratory epithelial cells through adhesion and cytotoxic effects. 2. M. pneumoniae causes damage to lungs and various systems of the whole body through immune response.

Damage to respiratory epithelium:

M. pneumoniae attaches to the ciliated respiratory epithelium at the base of the cilium through a complex terminal organelle consisting of interacting adhesins, chaperones (adhesin), and accessory proteins that aggregate at the tip of the organelle. M. pneumoniae is on one cell pole. Forms an adherent organelle that binds to the host cell surface and slides through a unique mechanism called an adherent organelle (Polarized attachment organelle).

MP attaches to bronchial epithelial cells through P1 adhesin, P30 adhesin, P40 protein, P90, P65, and high molecular weight (HMW) proteins (HMW1, HMW2, HMW4, HMW5). After P90 is synthesized and cleaved from the P40 protein, after maturation, two molecules of P1 adhesin and two molecules of P90 form an adhesin complex, and there are dozens of P1 adhesin complexes on the host cell surface. P30 does not directly affect the positioning of the P1 protein onto the apical structure, however, it interferes with the binding between P1 and its receptor [5]. The 170 kDa protein P1 adhesin, present on the surface of organelles, plays a key role in binding and sliding. Studies have shown that the recombinant P1 adhesin with 1476 amino

acid residues can be used for structural and functional studies and for the preparation of antibodies for medical applications [6]. P1 adhesins are highly antigenic and are targeted by the host's immune system. P1 adhesin exhibits sequence polymorphism among strains and may be involved in the escape of the host immune response. Topi is an important chaperone protein in the adhesion process of Mycoplasma pneumoniae that has the function of promoting the maturation of adherent organelles. HMW1, HMW2, HMW3, Topi, Lon, MPN387, P1, P400, and proteins A, B, and C, although not adhesins, appear to be critical for M. pneumoniae cell adhesion. The anti-P1 adhesin antibody specifically blocks the binding of Mycoplasma to the cell surface and reduces the sliding velocity of Mycoplasma pneumoniae. Adhesive organelles have tip structures, which are divided into internal structures and surface structures. The internal structure consists of three parts: terminal buttons, paired plates, and adhesin complexes, which are arranged in this order from the front of the cell and function as organelle formation, maintenance, and force generation and transmission. The membrane protrusion and sliding device at one end of the cell are called the terminal button. The terminal button changes the sliding direction of M. pneumoniae. The terminal button is composed of HMW3 and P65 proteins, and the average speed is 2.0 to 4.5 mm/s, or 3 to 3 of the cell length. 7 times, with a propulsion force of up to 113 pN, HWM3 plays a spatially organized role in assembly and function [7]. The internal structure is a "jellyfish"-like structure composed of 10 jellyfish structural proteins. Energy for motion is provided by ATP, which may remain in the form of ADP when gliding. It repeatedly captures, pulls, and releases sialylated oligosaccharides through a unique mechanism based on ATP energy, thereby sliding on solid surfaces. The glider is composed of a huge surface. A large structure composed of proteins and an inner jellyfish-like structure. The system may be due to adhesin, which developed from the fortuitous combination of the two and are essential for the adherent parasitic life of M. pneumoniae [8].

Cytotoxicity:

Studies have found that direct cytotoxicity and activation of inflammatory responses through Toll-like receptors lead to inflammatory cytokine-mediated tissue damage. The latest discovery is that the community-acquired respiratory distress syndrome toxin (the community-acquired respiratory distress syndrome CARDS toxin) has the ability to induce adenosine diphosphate (ADP) ribosylation and inflammation activation [9]. as well as some pathogenic factors of M. pneumoniae, such as hydrogen peroxide, nuclease, and lipid-associated membrane protein (Lipid-associated membrane protein, LAMPs).

Hydrogen peroxide:

M. pneumoniae produces hydrogen peroxide (H2O2) and superoxide radicals, which induce oxidative stress in respiratory epithelial cells [10]. M. pneumoniae is a pathogen of respiratory infection that adheres to and colonizes the surface of ciliated airway epithelial cells. Tight interactions between M. pneumoniae and its host cells contribute to persistent infection, and the host protects itself from mucociliary clearance. The clinical manifestations of respiratory diseases are due to the adhesion of M. pneumoniae to respiratory cells, which subsequently produces a variety of cell damage and induces inflammatory mediators to release cytokines from infected cells. Respiratory cells use epithelial cell shedding as a foothold for infection,

establish a defense mechanism against infectious microorganisms, and enable infected cells to eliminate pathogenic microorganisms from the focus of infection through the shed epithelial cells. Hydrogen peroxide is a metabolic by-product produced during the degradation of glycerol-3-phosphate by glycerol-3-phosphate dehydrogenase (GlpD). The cytotoxic effect of M. pneumoniae was significantly reduced due to GlpD deficiency. Studies have shown that M. pneumoniae may regulate hydrogen peroxide-induced polymerase-dependent and independent cell detachment in infected cells to use airway epithelial cells as a replication foothold and that M. pneumoniae has the ability to control exogenous hydrogen peroxide-induced epithelial cell detachment. Modulation of M. pneumoniae DNA damage-triggered signaling may be responsible for controlling detachment of infected cells [11].

CARDS (Community Acquired Respiratory Distress Syndrome) Toxin:

Bacterial toxins have specific mechanisms for binding and uptake by mammalian cells. M. pneumoniae CARDS (Community Acquired Respiratory Distress Syndrome) toxin is a 68 kDa protein with high binding affinity to human surfactant protein A and exhibits specific biological activities, including mono-ADP ribosylation and vacuolation change. These properties lead to airway inflammatory processes and a range of cellular pathologies, including ciliary arrest, loss of tissue integrity and damage, and cell death. However, the process by which CARDS toxins enter target cells is unclear. In this study, we found that the CARDS toxin binds to the surface of mammalian cells and rapidly internalizes in a dose- and time-dependent manner using a Clathrin-mediated pathway, as shown by inhibition of toxin internalization by monodansylcadaverine. But methyl--cyclodextrin did not inhibit toxin internalization or Filipino. Furthermore, the internalization of CARDS toxin was significantly inhibited in Clathrin-depleted cells.)

The CARDS toxin is an ADP-ribosylated vacuolating toxin homologous to the S1 subunit of pertussis toxin and has a high affinity for surfactant protein A, suggesting that the toxin has a physiological role in the lung. CARDS toxin is a protein that has recently been shown to be one of the main factors causing inflammation, and the longer the time and the higher the dose, the more severe the lung damage caused [12]. CARDS toxin is a key virulence determinant of M. pneumoniae. The N-terminus of the CARDS toxin has ADP-ribosyl transferase activity, while the C-terminus leads to cellular vacuolar activity. The disulfide bonds in CARDS toxins are essential for both maintaining the conformational stability of CARDS toxins and causing cytopathic effects [13]. CARDS toxin induces inflammation and histopathological damage associated with M. pneumoniae infection. Studies have shown that compared with common cases of MPP, in cases of refractory MPP, CARDS toxin, TNF-α, and IL-6 levels were significantly elevated in bronchoalveolar lavage fluid. In addition, CARDS toxin, IL-6 and TNF-α have good diagnostic ability for refractory M. pneumoniae pneumonia, CARDS toxin is positively correlated with TNF-α level in M. pneumoniae cases, TNF-α and TNF-α in BALF High co-expression of CARDS toxin is a good diagnostic biomarker to distinguish refractory M. pneumoniae pneumonia from common M. pneumoniae pneumonia in children [14].

Lipoprotein:

Lipid-associated membrane proteins (LAMPs) of M. pneumoniae are anchored to the cell membrane,

exposed extracellularly, and exert toxic effects on neighboring cells. The pathogenic mechanism of M. pneumoniae partly depends on its lipoprotein, which is expressed on the surface of Mycoplasma and plays an important role in the host immune inflammatory response [15]. Lipoproteins cause inflammation by promoting the production of immune factors.Lipoproteins from various Mycoplasma species have potent inflammatory properties, and more than 30 different Mycoplasma lipoprotein genes have been reported. The lipoprotein of M. pneumoniae can induce the expression of high-mobility group box protein 1 (HMGB1) in immune cells through the TLR2 pathway [16]. High-mobility group box protein 1 (HMGB1) is an actively secreted cytokine produced by macrophages and other inflammatory cells during innate immune responses to invasion. Mycoplasma-derived lipoproteins or their analogues activate lipopeptide 2 in macrophages to secrete lipopolysaccharide, which acts as a substance that stimulates the immune system and plays a key role in pathological damage during M. pneumoniae infection [17].

Laboratory testing methods for M. pneumoniae pneumonia:

Most *M. pneumoniae* infections in children are amenable to management on an outpatient basis, so physicians often rely on clinical suspicion and provide empiric treatment. However, a microbiologic diagnosis should be sought if illness is sufficient to warrant hospitalization, if there is unsatisfactory clinical response to initial antimicrobial therapy, if there are significant underlying comorbidities or immunosuppression that would make severe and disseminated disease more likely and if significant extrapulmonary symptoms are present[18].

Due to the prolonged turnaround time, specialized expertise required, limited availability and poor sensitivity, culture is rarely performed. Serology was the primary means for diagnosis for many years. Enzyme immunoassays (EIAs) are the most widely used serologic methods in many countries, although other methods such as particle agglutination assays and immunofluorescence are also used [19]. EIAs can be performed with very small volumes of serum to provide isotype-specific data for IgM, IgG and IgA. Rapid EIAs for IgM have been developed for detection of acute infection using a single serum specimen. However, one such EIA had a sensitivity of only 31.8% when a single serum sample was analyzed from Japanese children with pneumonia, increasing to 88.6% when paired acute and convalescent sera were analyzed [20]. Evaluations of commercial EIAs and particle agglutination assays using PCR as a reference have found that most assays have problems with sensitivity and specificity, especially if only a single specimen is analyzed. IgA may rise more quickly and decline sooner than IgM or IgG. However, a recent evaluation of a commercial IgA assay in our laboratory detected no IgA-positive specimens from patients with pneumonia who were culture- and/or PCR-positive for *M. pneumoniae* and who were not also positive for IgM. A combination of IgM or IgA and PCR has been suggested as an optimum diagnostic approach but would add considerable cost to laboratory testing. Due to the imperfect immune function of infants and young children, the positive detection rate of MP-IgM for M. pneumoniae varies between different age groups, and laboratory results need to be comprehensively evaluated. IgM antibodies are produced after infection and rise within 6 to 10 days of infection. These antibodies peak after 3 to 6 weeks and then gradually decline but may remain positive for

weeks to months. Antibiotic drug treatment will not shorten the duration of antibody positivity, and it is meaningless to evaluate the therapeutic effect [21]. Nowadays, many new technologies are used for the detection of M. pneumoniae, such as loop-mediated isothermal amplification (LAMP), dual-primer isothermal amplification (DAMP) and recombinase-assisted amplification. (Recombinase-aided amplification, RAA) analysis, the recombinase-assisted amplification (RAA) assay is a recently developed rapid detection method that has been used to detect a variety of pathogens. Recombinase UvsX from E.coli, single-stranded DNA binding protein, and DNA polymerase are combined in a RAA reaction system. UvsX recombinase and primers form protein-DNA complexes that bind to homologous sequences in double-stranded DNA targets. Once the homologous sequence is located by the primer, a strand exchange reaction occurs to initiate DNA synthesis, and the target region on the template is exponentially amplified. The amplification process is completed within 15-30 min at 39°C [22,23]. Recombinase-assisted amplification (RAA), RAA primers and probes are designed based on the P1 gene, and RAA analysis still has some limitations. First, it is currently difficult to perform multiplex amplification of different targets in RAA, because the primers of RAA each require more than 30 bp of complementary sequence, while the probe requires about 50 bp, and more and more primers will lead to non-specific amplification, this limits the development of multiplex RAA assays. Second, RAA cannot distinguish between colonization and true infection, nor can it be co-infected with other pathogens [24]. Combining loop-mediated isothermal amplification (LAMP) with a nanoparticle-based lateral flow biosensor (LFB) assay, the MP-LAMP-LFB assay, which specifically identifies DNA templates for MP, obtained no cross-reactivity with other pathogens. LAMP-LFB detection is a simple, objective, and sensitive MP detection method that can be widely used in clinical settings, especially in township health centres [25]. Due to the increased target sites, current LAMP methods, especially LAMP with two loop primers, suffer from non-specific amplification due to strong background signals. This non-specific amplification greatly reduces the reliability of LAMP and limits its application in clinical diagnosis [26].

Clinical manifestations of M. pneumoniae pneumonia:

Mycoplasma pneumoniae infection can occur in infants and even newborns, but the peak incidence is in preschool and school-age children. Since infants and young children produce a lower immune response, MP infection in young children mostly manifests as mild or subclinical infection, resulting in a low detection rate of M. pneumoniae in infant and young children. Mycoplasma pneumoniae mainly causes respiratory tract infections, and cough is the most common symptom, accounting for 90% to 100% of patients. The cough can last 3 to 4 weeks and may or may not be associated with wheezing. Patients may also report headache (60%-84%), sore throat (6%-59%), nasal symptoms (2%-40%), and earache (2%-35%), Therefore, if children around 5 years old have a persistent high fever and severe cough, SMPP should be considered [27]. Children who experience chest pain are twice as likely to be infected with M.pneumoniae. In the early stage, rough breathing and low breath sounds appear on lung auscultation. In the later stage, lung ventilation improves, and fixed moist rales may appear. There are also cases of stridor. However, most of the lung signs of M. pneumoniae pneumonia are not obvious. This may be also the cause of Mycoplasma pneumoniae pneumonia.

The main reason for missed diagnosis of pneumonia is that children with long-term fever and cough need to be alert to the possibility of MPP. Yan et al. [28], analysed 433 children with SMPP and found that 75.9% of the children would develop complications, and pleural effusion and pulmonary consolidation were the most common. At present, there are more and more reports of extrapulmonary diseases related to Mycoplasma pneumoniae, among which virulence factors, M. pneumoniae Persistent injury, antimicrobial resistance, and host immunological profiles interact in complex ways.

Imaging manifestations of MPP:

Chest radiographs play an important role in assessing a patient's current condition and prognosis and in determining a treatment plan. Imaging findings vary widely and are characterized primarily by lobar parenchymal infiltrates and atelectasis but may also present as persistent pleural effusion or segmental atelectasis, with some fusion into sheets and pleural effusion. The most common chest X-ray findings are lobar parenchymal infiltrates, patchy infiltrates, focal reticular nodular infiltrates, interstitial changes, and perihilar bronchial infiltrates. Lobar parenchymal infiltrates are defined as uniform, dense, high-density infiltrates. The pulmonary vessel shadow is blurred and involves multiple lung segments. Plaque infiltration was defined as ground-glass lesions involving multiple bronchiolar segments. Localized reticular nodular infiltration is defined as high-density reticular nodules that do not involve the entire lung lobe. Peri bronchial infiltrate is defined as extensive hilar reticulonodular disease involving most of the lung lobes. CT images may show bronchial wall thickening, bronchiectasis, air bronchus sign, etc. Typical histopathological features are edematous and ulcerated bronchial and bronchiolar walls, which are infiltrated by macrophages, lymphocytes, neutrophils, and plasma cells. In severe pneumonia, the cell-mediated immune response is more intense and interleukin levels are elevated, leading to diffuse alveolar damage with fibrinous exudates in alveolar lumens, which appear as lobar parenchymal infiltrates on radiographs [29]. Studies have shown that lobar parenchymal infiltration is the most common manifestation in M pneumoniae pneumonia, the incidence of pleural effusion is also high, and necrotizing pneumonia may occur. Older children are more likely to have lobar parenchymal infiltrates and have a longer duration of fever [30]. A chest X-ray of atelectasis shows that the light transmittance of the lesion is reduced. Atelectasis in M. pneumoniae is usually an acute disease. Initially, atypical symptoms may appear, such as fever and an irritating dry cough, or general discomfort such as fatigue and headache. Important feature of atelectasis. Some studies have shown that fever may be a risk factor for MP pneumonia complicated by atelectasis. In addition to the factors of M. pneumoniae infection itself, the high fever observed in M.pneumoniae infection may be related to the enhancement of cellular immunity [31]. Absorption is slow after pulmonary consolidation, which generally takes 4 weeks, and complete absorption takes 8 weeks. The clinical course is not determined by the absorption of pulmonary consolidation, but regular review is required to prevent secondary infection with Mycoplasma pneumoniae.

Treatment of MPP:

Macrolide antibiotics are recognized worldwide as the first choice for M. pneumoniae infections. The

course of antibiotic treatment is determined based on the disappearance of the child's clinical symptoms and signs, a decrease in inflammatory indicators, and an improvement in imaging findings. There are also reports of effective treatment with tetracycline antibiotics and quinolone antibiotics in children with macrolide resistance, but considering their adverse reactions to children, they are not recommended in clinical practice. To reduce the incidence of SMPP and RMPP, caution needs to be taken against the misuse of antibiotics. Glucocorticoids can reduce the host immune response to Mycoplasma pneumoniae, improve clinical features, and reduce lung damage in children and adults. They can reduce lung histopathological damage by reducing cytokines and inflammatory responses, ultimately reducing mortality. Combining glucocorticoids to treat MPP can significantly shorten the duration of fever and hospitalization and reduce CRP levels [32]. Youn and Lee5 proposed early administration of corticosteroids to children with MPP who presented with respiratory distress at admission or who had a fever that persisted for more than 48 hours after admission to prevent the development of SMPP in some children, but overuse of steroids should be avoided [33]. Antibiotics may have limited efficacy in MP infection, whereas early corticosteroid treatment may reduce disease morbidity and prevent the progression of extrapulmonary complications [34]. Compared with low-dose methylprednisolone, high-dose methylprednisolone can significantly shorten the time for antipyretic therapy, disappearance of pulmonary rales, disappearance of cough, and absorption of lung shadows, and reduce hospitalization time and hospitalization costs. High-dose methylprednisolone can effectively treat severe MPP without increasing the incidence of adverse reactions. Clinical studies have confirmed the effectiveness of glucocorticoids in children with refractory MPP. Most studies typically use methylprednisolone 1-2 mg/kg/d over 3-5 days. Other studies have confirmed that methylprednisolone 10-30 mg/kg/d for 3-5 days has achieved good clinical efficacy [35]. One study [36] defined SMPP with persistent or recurrent fever for >72 hours after treatment with methylprednisolone (2 mg/kg/d) as glucocorticoid resistant SMPP. This study found that fever duration ≥11 days, lymphocyte Percentage ≤ 32%, CRP ≥ 48.73 mg/L, and LDH ≥ 545.7 IU/L are risk factors for glucocorticoid resistance. In this case, you can consider increasing the dose of hormones and intravenously injecting methylprednisolone every day. 4 mg/kg, increasing to 6 mg/kg/day if fever persists. For the treatment of SMPP, there is no uniform standard for the use and dosage of glucocorticoids. Therefore, long-term and large-scale studies are necessary to further standardize it. Gamma globulin (IVIG) has immunomodulatory and anti-inflammatory effects. Azithromycin combined with IVIG has better clinical therapeutic effects in the treatment of children with SMPP, can shorten the course of the disease, and improve the prognosis. After appropriate antibiotic therapy fails, when imaging shows lobar, segmental consolidation, or atelectasis, fiberoptic bronchoscopy can be performed and treated. In recent years, M. pneumoniae has become the main pathogen of community-acquired pneumonia in children. Cases of serious complications, treatment difficulties, and adverse clinical outcomes have increased. Extrapulmonary manifestations involve multiple systems throughout the body, and some have extrapulmonary manifestations as the first symptom, making diagnosis difficult, which needs to be paid more attention by clinicians. New technology for M. pneumoniae infection.

SUMMARY

To sum up, the pathogenesis of SMPP in children is not yet very clear. At present, it is believed that MP resistance, immune disorder, mixed infection, blood hypercoagulability, CARDS Tx, etc., contribute to SMPP's diverse clinical manifestations, long course of disease, and rapid progression. . Treatment the above is mainly comprehensive treatment; macrolide drugs can be combined with other antibiotics and hormone therapy; drug-resistant patients can be replaced by alternative antibiotics such as tetracyclines or fluoroquinolones; and glucocorticoid-resistant patients can be added with IVIG or other drugs. Immunomodulators, while the use of bronchoalveolar lavage has increased in recent years, and the effect is significant. Clarify the pathogenesis of SMPP in children, detect and treat SMPP early, shorten the course of the disease, improve clinical efficacy, and improve the prognosis of children. At present, there are various clinical treatment options for SMPP; there is no unified treatment plan; and there are also differences in the course of treatment and dosage. The optimal drug, dosage, and course of treatment for SMPP need further research.

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