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Review Article

# Mycoplasma Pneumoniae as a Causative Agent of Community-Acquired Lower Respiratory Tract Infections in Children

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**Abstract**

*Mycoplasma pneumoniae (M. pneumoniae)* causes respiratory tract infections in all age groups but older children and young adults are more affected than other age groups. Atypical pneumonia was described as a distinct and mild form of community-acquired pneumonia (CAP) already before *M. pneumoniae* had been discovered and recognized as its cause. *M. pneumoniae* is estimated to be the cause of up to 40% of community acquired pneumonia in children over 5 years of age. Extrapulmonary manifestations have been reported in almost every organ. The correct diagnosis of *M. pneumoniae* infections is critical to initiate the appropriate therapy, since it is not possible to diagnose *M. pneumoniae* infection merely based on clinical signs and symptoms. Empirical therapy is, therefore, given in most cases. The current methods for diagnosing *M. pneumoniae* infection can be achieved using culture, serology, or molecular-based methods.Mycoplasmas do not have cell wall so are not susceptible to β-lactam antimicrobial drugs, macrolides are generally accepted as first choice agent for treatment, especially in children. Emergence of macrolide resistant *M. pneumoniae* is now being reported in children, in more than 95% of *M. pneumoniae* isolates, which may be associated with severe clinical features and more extrapulmonary complications. This review focuses on the many new developments that enhance our understanding of *M. pneumoniae* causing community-acquired lower respiratory tract infections in children

## INTRODUCTION

Lower respiratory tract infections are considered a common cause responsible for morbidity and mortality among children [1].The clinical entity of "atypical" pneumonia" was identified well prior to the establishment of *Mycoplasma pneumoniae* (*M. pneumoniae)* as its etiology agent. In 1937, Dienes and Edstall [2] isolated the first human "mycoplasma" from an abscess in a Bartholin's gland [3,4]. In 1944, Eaton et al. first isolated *M. pneumoniae* in tissue culture from a sputum sample from a patient with primary "atypical pneumonia"; was named Eaton agent [5]. At that time, it was thought to be a virus because it was resistant to penicillin and sulfonamides and passed through filters that retained bacteria. Chanok et al.[6], proposed the taxonomic name *M. pneumoniae* for Eaton agent in 1962 [3].

Mycoplasmas are the smallest known free-living prokaryotes, with an extremely small genome size of 580to 2200 kilobase pair [1] lacking a cell wall. The absence of a cell wall and the specialized attachment organelle facilitates close contact with the host's respiratory epithelium, supplying the bacterium with nutrients necessary for its growth and proliferation.

*M. pneumoniae* is capable of infecting both the upper respiratory tract and lower respiratory tract. Clinical manifestations of *M. pneumoniae* can occur as mild cases of tracheobronchitis to severe atypical pneumonia that can lead to various extrapulmonary complications [8]. *M. pneumoniae* has been identified as the cause of up to 40% of community-acquired pneumonia (CAP) cases in children over 5 years old [1].

The correct identification of *M. pneumoniae* infections is critical for prescription of the appropriate therapy since since it is not possible to diagnose *M. pneumoniae* infection merely based on clinical signs and symptoms. In only a minority of cases, specific aetiologic diagnosis of *M. pneumoniae* infection is established [9]. Mycoplasmas do not have cell wall so are not susceptible to β-lactam antimicrobial drugs, macrolides are generally accepted as first choice agent for treatment, especially in children. A worldwide increase in the prevalence of macrolide resistant *Mycoplasma pneumoniae* (MRMP) strains has been witnessed since 2000 .In some regions of Asia, the resistance rates have been reported to be over 90% [10]. Since molecular-based assays can detect *M. pnueumoniae* in clinical specimens, there is a need for real point of care testing for fast detection of *M. pneumoniae* or its DNA and mutations in macrolide resistance gene. It is necessary to develop safe vaccines that provide protective immunity against

*M. pneumoniae* infection. *M. pneumoniae* should be considered in differential diagnosis of CAP and additionally it should also be considered in co-infections which are unresponsive to commonly administered beta-lactams [11,12].

This review focuses on the many new developments that enhance our understanding of *M. pneumoniae* causing community-acquired lower respiratory tract infections in children.

## Epidemiology of Mycoplasma pneumoniae infections

*M. pneumoniae* can cause both upper and lower respiratory tract infections and is endemic and epidemic worldwide in children and adults. It is primarily a disease of childhood and adolescence, with the peak incidence of infection between 5 and 15 years of age. It may be responsible for approximately about 4 to 8% of community-acquired bacterial pneumonia (CABP) cases during endemic periods, up to 20 to 40% of CABP in the general population during epidemics, increasing up to 70% in closed populations [7].

*M. pneumoniae* infection spreads through droplets released from the upper and lower respiratory tract and can survive in the respiratory tract for several weeks or several months with an incubation period 1to 3 weeks. Infections tend to be more common in the summer or early fall, but can occur at any time of the year. Epidemics occur primarily during *M. pneumoniae* epidemic cycles, in addition to endemic background patterns [13]. The cyclical epidemics (every few years) of *M. pneumoniae* are associated with a shift from one P1subtype to another [14,15]. Outbreaks have been reported in the closed populations (e.g. summer camps, schools, military bases, college dormitories). *M. pneumoniae* can also cause nosocomial infections in long-term care (LTC) facilities. Natural immunity to *M. pneumoniae* infections is usually short-lived and a failure of natural immunity to eliminate the organisms, leads to prolonged carriage in some instances.

## Clinical Manifestations Respiratory Disease

Most *M. pneumoniae* infections are symptomatic, and most of these occur in children and adolescents. *M. pneumoniae* often causes tracheobronchitis, which manifests as a dry cough or a cough that produces mucoid or mucopurulent sputum. Many individuals may develop nonspecific symptoms that resemble an upper respiratory tract infections, such as coryza, sore throat, headache, and otitis media. In more serious cases, dyspnoea may occur, and the cough may have pertussis-like characteristics [1].

Coryza and wheezing are most likely to occur in children under five years of age, while the development of pneumonia is relatively rare. Bronchopneumonia (with one or more lobes) occurs in children aged 5 to 15 years and may require hospitalization [16]. The term “walking pneumonia” or “primary atypical pneumonia” is used to characterize the mycoplasmal respiratory disease that is characteristic of *M. pneumoniae* because the disease is mild, non-debilitating, and presents with the onset of pneumonic symptoms, and patient still continues to function mostly normal [1].

The clinical presentation of respiratory disease caused by *M. pneumoniae* is indistinguishable from other atypical pathogens, notably many respiratory viruses, *Chlamydophila pneumoniae* and *Streptococcus pneumoniae*. *M. pneumoniae* causes cough, fever and unilateral crackles. Chest auscultation may reveal coarse rales and rhonchi if the disease is limited to tracheobronchitis and fine inspiratory rales and dullness at the base of the lungs if pneumonia has developed. It is often difficult to distinguish *M. pneumoniae* pneumonia from viral pneumonia clinically, so this has influenced the recommendations for the use of antibiotics in the treatment of pneumonia in children [17].

Radiographically, *M. pneumoniae* infections may be indistinguishable from a viral lower respiratory tract infections, with patchy airspace consolidation and ground-glass opacities. The more obvious radiographic abnormalities are often in the lower lobes. Unilateral pleural effusions are especially common in children.

## Asthma

*M. pneumoniae* infection is associated with asthma. The infection may precede asthma onset, exacerbate the asthma [18], or play a role in chronic asthma in some children and adults. Extrapulmonary manifestations, *M. pneumoniae* can cause extrapulmonary manifestations in almost every organ, including the skin, hematologic, cardiovascular, musculoskeletal, and nervous systems. The most common manifestations are dermatological and neurological system illnesses. These extrapulmonary manifestations may be caused by three different mechanisms such as direct local effects of bacteria, by indirect effects or after bacterial dissemination [19].

The most common manifestations are dermatological and neurological system illnesses. Skin complications may occur in up to 25% of patients such as erythema multiforme, anaphylactoid purpura Stevens–Johnson syndrome and urticaria. *M. pneumoniae* is the most common cause of encephalitis in children, accounting for up to 13% of cases [20]. There are also other neurological complications such as Guillain-Barre Syndrome (ascending paralysis) and acute demyelinating encephalopathy [8].

It can also cause autoimmune hemolytic anemia, septic arthritis, rhabdomyolysis and rarely plays a role in cardiac manifestations. Other nonspecific symptoms, such as conjunctivitis, iritis, and uveitis, may have an immunological basis, as no pathogens were detected in ocular tissue [21].

## Carriage

Like many other respiratory pathogens, *M. pneumoniae* can be carried asymptomatically in the respiratory tract. The detection rate of *M. pneumoniae* DNA in the respiratory tract of healthy children without respiratory symptoms was 21% in a Dutch study [22], and 56% in an American study [23]. In children with

*M. pneumoniae* CAP, co-existence of *M. pneumoniae* with other pathogens has also been described, and was recently reported in 28% of the patients [24].

## Laboratory Diagnosis

The current methods for diagnosing *M. pneumoniae* infection can be achieved using culture, serology, or molecular-based methods.

### A. Culture

Culture methods have been the gold standard for diagnosis but is time-consuming, laborious and expensive and colonies become visible in 2-5 weeks, therefore, for routine diagnosis is not recommended.

### B. Serology

Serum testing is more sensitive than culture for detecting *M. pneumoniae* infection.

## Cold Agglutinins

Cold agglutinin testing was once considered a valuable tool, but it is not a highly specific indicator of *M. pneumoniae*. Cross-reacting cold agglutinins are produced in about 50% of *M. pneumoniae* infections and disappears within 6 to 8 weeks.

## Complement fixation test (CFT)

The complement fixation test (CFT) to detect antibodies against *M. pneumoniae* lacks sensitivity and specificity and has been replaced by alternative methods.

## Detection of Mycoplasma pneumoniae-Specific Antibodies

The most reliable serological diagnosis of *M. pneumoniae* is when antibody titers of 4-fold or greater are detected in paired serum samples obtained 2 to 3 weeks apart and tested concurrently for IgM and IgG antibodies [3]. The most widely used serological methods are enzyme-linked immunosorbent assays (ELISA) to detect immunoglobulin M (IgM), IgG, and IgA antibodies to *M. pneumoniae*, although other methods e.g. particle agglutination (PA) assays and immunofluorescence methods were also used.

### C. Detection of *Mycoplasma pneumoniae*-Specific Nucleic Acids

Nucleic acid amplification techniques (NAATs) have the potential to provide rapid, sensitive and specific results and can support appropriate early antibiotic treatment. With higher analytical sensitivity and shorter turnaround times, NAAT is increasingly considered the "new gold standard". They are available with a great variation of methods used, including variability of target, NAAT (conventional, nested, real-time; monoplex vs. multiplex; polymerase chain reaction (PCR) vs. isothermal amplification technologies), detection formats, and different platforms. The main gene targets used in PCR assays to detect *M. pneumoniae* are the P1adhesin gene, ATPase operon, CARDS toxin gene,16S-23rRNA spacer,16S rRNA, dnaK, pdhA, tuf, parE, ptsL, and the noncoding repetitive element in repMp1 [25,26]. Conventional PCR for *M. pneumoniae* has mostly been replaced by real-time PCR. NAAT is not recommended in children not suspected of having typical manifestations of mycoplasmal infection [24]. Besides PCR, other NAAT formats include loop-mediated isothermal amplification (LAMP), nucleic acid sequence-based amplification (NASBA), and strand displacement assay (SDA).

### D. Non-amplified antigen detection

Immunochromatographic (lateral flow) assay is used for pathogen detection at the point of care. Another immunochromatographic assay used colloidal gold to detect *M. pneumoniae* (P1 gene) with 100% sensitivity and 97.4% specificity compared to real-time PCR. NA-SERS-NA-SERS (Nanorod array surface-enhanced Raman spectroscopy) is a new research method for the detection of *M. pneumoniae* [27]. The Raman signal enhancement permits the acquisition of unique SERS spectra within seconds without the need for sample amplification by growth or PCR [28].

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) potentially limits its usefulness for *M. pneumoniae* due to the time-consuming and insensitive nature of the prerequisite culture in order to perform MALDI-TOF MS.[25].

## Treatment and Macrolide-resistant Mycoplasma pneumoniae

*M. pneumoniae* lacks a cell wall. Hence it is insensitive to the penicillins and other β-lactam antibiotics. In children with *M pneumoniae* infection, macrolides are recommended as first line antibiotic treatment [3]. Quinolones are still not recommended for use in children, although ciprofloxacin has been shown to be safe in children. In the early 2000s, the emergence of *Macrolide-resistance Mycoplasmasa pneumoniae* (MRMP) was observed in Japan due to point mutations in the peptidyl-transferase loop of the 23S rRNA, most commonly the A2063G mutation, which then spread to Asia, Europe, and North America (8). Quinolones, tetracyclines or glycylcyclines tigecyclines [29], may lead to clinical improvement after failure of macrolide therapy in children.

## Vaccination

There is currently no vaccine to protect against *M. pneumoniae* infections. Various types of *M. pneumoniae* vaccines include inactivated, live-attenuated, and subunit vaccines [30]. Human vaccine has yet to develop a vaccine suitable for general use, specifically targeting the emergence of MRMP.

# CONCLUSIONS

*M. pneumoniae* can cause respiratory infections in

persons of all ages and can account for a significant portion of community acquired bacterial pneumonia (CABP), especially during epidemics. Extrapulmonary manifestations have been reported in almost every organ. With molecular tests capable of detecting *M. pneumoniae* in clinical samples with same-day turnaround, diagnostic laboratories can now provide improved microbiological diagnosis, but quick detection of *M. pneumoniae* or its DNA, as well as mutations in the macrolide resistance gene, requires real point-of-care testing. Antibiotics are urgently needed for the implementation of MRMP therapy that can be used safely in children. Clinicians managing patients infected with COVID-19 should be alert to *M. pneumoniae* coinfection, which may exacerbate clinical symptoms during this COVID-19 outbreak. Development of a safe vaccine would provide protective immunity and would be an important step in reducing the level of *M. pneumoniae* infection.

## TRANSPARENCY DECLARATION

### Contribution

**Surinder Kumar:** Concept and design of the study; Writing–Writing original draft, revision, and final approval of the version. **Sourabh Kumar:** Concept and design of the present study,Writing- Participated in original draft, revision, final approval of the version.

## REFERENCES

1. Kumar S. Mycoplasma pneumoniae: A significant but underrated pathogen in paediatric community- acquired lower respiratory tract infections. Indian J Med Res. 2018; 147: 23- 31.
2. Dienes L, Edstall G. Observations on the L-organisms of Klieneberger. Proc Soc Exp Biol. 1937; 36: 740-774.
3. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. Clin Microbiol Rev. 2004; 17: 697-728.
4. Domingues D, Nogueira F, Tavira L, Exposto F. Mycoplasmas: What is the role in human infections? Acta Med Port. 2005; 18: 377-383.
5. Eaton MD, Meiklejohn G, van Herick W. Studies on the etiology of primary atypical pneumonia: A filterable agent transmissible to cotton rats, hamsters, and chick embryos. J Exp Med. 1944; 79: 649-668.
6. Chanok RM, Dienes L, Eaton MD, Edward DGA, Freundt EA, Hayflick L, et al. Mycoplamsa pneumoniae: Proposed nomenclature for atypical pneumonia organisms (Eaton agent). Science. 1963; 140: 662.
7. Kumar S, Kumar S. Mycoplasma pneumoniae: Among the smallest bacterial pathogens with great clinical significance in children. Indian J Med Microbiol. 2023; 46: 100480.
8. Atkinson TP, Waites KB. Mycoplasma pneumoniae infections in childhood. Pediatr Ifect Dis. ..2014; 33: 92-94.
9. Kumar S, Saigal SR, Sethi GR. Rapid diagnosis of Mycoplasma pneumoniae by polymerase chain reaction in community-acquired lower respiratory tract infections. Trop Doct. 2011; 41: 160-162.
10. Zhou Z, Li X, Chen X. Macrolide-resistant mycoplasma pneumonia in adults in Zhejiang, China. Antimicrob Agents Chemother. 2015; 59: 1048-1051.
11. Hammerschlag MR. Mycoplasma pneumoniae infections. Curr Opin Infect Dis. 2001; 14: 181-186.
12. Korppi M. Community-acquired pneumonia in children: Issues in optimizing antibacterial treatment. Paediatr Drugs. 2003; 5: 821-832.
13. Jacobs E. Mycoplasma pneumoniae: now in the focus of clinicians and epidemiologists. Euro Surveill. 2012; 17: 20084.
14. Dumke R, Catrein I, Herrmann R, Jacobs E. Preference, adaptation and survival of Mycoplasma pneumoniae subtypes in an animal model. Int J Med Microbiol. 2004; 294: 149-155.
15. Jacobs E, Ehrhardt I, Dumke R. New insights in the outbreak pattern of Mycoplasma pneumoniae. Int J Med Microbiol. 2015; 305: 705-708.
16. Waites KB. New concepts of Mycoplasma pneumoniae infections in children. Pediatr Pulmonol. . 2003; 36: 267-278.
17. British Thoracic Society Standards of Care Committee. British thoracic society guidelines for the management of community acquired pneumonia in childhood. Thorax. 2002; 57: i1-24
18. Kumar S, Roy RD, Sethi GR, Saigal SR. Mycoplasma pneumoniae infection and asthma in children. Trop Doct. 2019; 49: 117-119.
19. Narita M. Classification of extrapulmonary manifestations due to Mycoplasma pneumoniae infection on the basis of possible pathogenesis. Front Microbiol. 2016; 7: 23.
20. Stamm B, Moschopulos M, Hungerbuehler H, Guarner J, Genrich GL, Zaki SR. Neuroinvasion by Mycoplasma pneumoniae in acute disseminated encephalomyelitis. Emerg Infect Dis. 2008; 14: 641-643.
21. Narita M. Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia. J Infect Chemother. 2010; 16: 162-169.
22. Spuesens EB, Fraaij PL, Visser EG, Hoogenboezem T, Hop WC, van Adrichem LN, et al. Carriage of Mycoplasma pneumoniae in the upper respiratory tract of symptomatic and asymptomatic children: an observational study. PLoS Med. 2013; 10: e1001444.
23. Wood PR, Hill VL, Burks ML, Peters JI, Singh H, Kannan TR, et al. Mycoplasma pneumoniae in children with acute and refractory asthma. Ann Allergy Asthma Immunol. 2013; 110: 328- 334.e1. Erratum in: Ann Allergy Asthma Immunol. 2013; 111: 309.
24. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015; 372: 835-845.
25. Waites KB, Xiao L, Liu Y, Balish MF, Atkinson TP. Mycoplasma pneumoniae from the respiratory tract and beyond. Clin Microbiol Rev. 2017; 30: 747-809.
26. Z, Li X, Chen X, Yao L, Pan C, Huang H, Luo F, et al. Comparison of P1 and 16S rRNA genes for detection of Mycoplasma pneumoniae by nested PCR in adults in Zhejiang, China. J Infect Dev Ctries. 2015; 9: 244-253.
27. Henderson KC, Benitez AJ, Ratliff AE, Crabb DM, Sheppard ES, Winchell JM, et al. Specificity and strain-typing capabilities of Nanorod array-surface enhanced Raman spectroscopy for Mycoplasma pneumoniae detection. PLoS One. 2015; 10: e0131831.
28. Patel IS, Premasiri WR, Moir DT, Ziegler LD. Barcoding bacterial cells: a SERS based methodology for pathogen identification. J Raman Spectrosc. 2008; 39: 1660-1672.
29. To KK, Chan KH, Fung YF, Yuen KY, Ho PL. Azithromycin treatment failure in macrolide-resistant Mycoplasma pneumoniae pneumonia. Eur Respir J. 2010; 36: 969-971.
30. Jiang Z, Li S, Zhu C, Zhou R, Leung PHM. Mycoplasma pneumoniae Infections: Pathogenesis and Vaccine Development. Pathogens. 2021; 10: 119.