Journal of Infection (2017) 74, S95—S100

ELSEVIER

BIA
British Infection Association

www.elsevierhealth.com/journals/jinf

# Things that could be *Mycoplasma pneumoniae*

**Ruben C.A. de Groot [a], Patrick M. Meyer Sauteur [a,b], Wendy W.J. Unger [a], Annemarie M.C. van Rossum [c,*]**

[a] *Laboratory of Pediatrics, Erasmus MC-Sophia Children's Hospital, University Medical Center, Rotterdam, The Netherlands*
[b] *Division of Infectious Diseases and Hospital Epidemiology, and Children's Research Center (CRC), University Children's Hospital of Zurich, Zurich, Switzerland*
[c] *Department of Pediatrics , Division of Pediatric Infectious Diseases, Immunology and Rheumatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands*

Available online 23 June 2017

**KEYWORDS**
*Mycoplasma pneumoniae*;
Respiratory tract diseases;
Stevens-Johnson syndrome;
Guillain-Barré syndrome;
Encephalitis;
Cold agglutinin disease;
Infectious arthritis;
Serological test;
Macrolides

**Summary** *M. pneumoniae* infection gives rise to a wide variety of manifestations. The pathogenesis of secondary manifestations is not always known. Some depend on the direct invasion of *M. pneumoniae* and others on the indirect effect of *M. pneumoniae* through pathological immune responses, for instance autoreactive antibodies in Guillain-Barré Syndrome. Diagnosis remains challenging with currently available diagnostic tests, because they do not demonstrate a causal relation due to *M. pneumoniae* asymptomatic carriage or previous infection. The mainstay of treatment is macrolide antibiotics, but the role of additional immunomodulation therapy is unclear. Knowledge of the pathogenesis of the different manifestations should guide strategies for diagnosis and treatment.


## Background

In the 1940s, *Mycoplasma pneumoniae* was discovered to cause atypical pneumonia. The pathogen, first named Eaton agent, was then believed to be a virus since it passed through bacterial filters.[1,2] Later research showed that this was due to its small size. *M. pneumoniae* is one of the smallest free-living bacteria with a length of 0.2 μm. Although *M. pneumoniae* is free-living, in order to survive in humans, it needs to access

* Corresponding author. PO Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 704 0704.
E-mail addresses: r.degroot@erasmusmc.nl (Ruben C.A. de Groot), Patrick.Meyer@kispi.uzh.ch (Patrick M. Meyer Sauteur), w.unger@erasmusmc.nl (Wendy W.J. Unger), a.vanrossum@erasmusmc.nl (A.M.C. van Rossum).

host-derived nutrients because of its limited metabolic capability. To access the nutrients *M. pneumoniae* colonizes the respiratory tract by adhering to ciliated epithelium using its tip organelle containing the P1 adhesion protein. *M. pneumoniae* employs different toxins during infection such as the CARDS-toxin.[3] Another distinguishing feature of *M. pneumoniae,* which is shared with other members of the class of Mollicutes, is the lack of a cell wall that renders them insensitive to beta-lactam antibiotics.

*M. pneumoniae* is well known to cause respiratory tract disease but extra pulmonary manifestations are also common and can be severe. The pathogenesis of these extra pulmonary manifestations may be diverse and are most probably not directly caused by the organism itself, but rather by the host immune response. Knowledge of these differences in pathogenesis allows a tailored choice in using diagnostic tests and treatment options. In this review, we will describe both the pathogenesis and clinical characteristics of the different manifestations of *M. pneumoniae* infection to aid clinicians in their often challenging diagnosis and treatment.

## The respiratory tract is the primary site of *M. pneumoniae* infection and carriage

The presence of *M. pneumoniae* in the respiratory tract can denote three different stages of infection: (i) asymptomatic carriage in the upper respiratory tract, (ii) symptomatic upper respiratory tract infection, and (iii) symptomatic lower respiratory tract infection. Although upper respiratory tract infection is less investigated, a study where volunteers were inoculated with *M. pneumoniae* shows that almost half of patients developed upper respiratory tract infections such as otitis media.[4] Most research and the rest of this paragraph however is focused on lower respiratory tract infection as major burden of disease. The epidemiology of lower respiratory tract infections has changed since the implementation of pneumococcal vaccination. *M. pneumoniae* is now the most common bacterial cause of community-acquired pneumonia requiring hospitalization in children. This percentage rises to 16% and 23% in children aged 5–9 years and 10–17 years, respectively.[5] *M. pneumoniae* pulmonary infections may be more common in asthma patients, could lead to asthma exacerbations, and have also been implicated as a trigger for the development of adult onset asthma.[6,7]

### Pathogenesis

Upon acquisition by a patient, *M. pneumoniae* can asymptomatically colonize the upper respiratory tract. This may be a common event since a study of healthy children showed that 21.2% carried *M. pneumoniae* in the upper respiratory tract as evidenced by *M. pneumoniae*-specific PCR.[8] Close contact may be needed for the spread of *M. pneumoniae* since outbreaks occur in families and amongst military recruits. Children are thought to be a reservoir from which transmission to other family members can occur. Why some children subsequently develop lower respiratory tract infection and others do not is unknown, but likely it is a multifactorial process dependent on both pathogen and host specific factors. Lower respiratory tract infection is characterized by disruption of the bronchial epithelium and evokes the production of cytokines such as TNF-α, IL1-β, IL-6, and IL-8.[9] Histology shows peribronchial infiltration of mainly neutrophils and also macrophages in mouse models as well as humans.[10,11]

### Clinical presentation

Lower respiratory tract infection caused by *M. pneumoniae* presents differently from pneumonia caused by pneumococcus: it presents less acutely, frequently has flu-like symptoms such as headache and myalgia and usually gives a milder but protracted disease.[4,12] *M. pneumoniae* lower respiratory tract infection is usually self-limiting and patients recover completely. However, severe disease with respiratory insufficiency due to Acute Respiratory Distress Syndrome (ARDS) has been described. The clinical presentation of *M. pneumoniae* is similar to viral infections and usually cannot be discerned on the basis of clinical characteristics alone. Duration of fever longer than two days and age four or older however does make *M. pneumoniae* more likely to be the causative pathogen.[13]

### Diagnosis

The gold standard test of *M. pneumoniae* infection is a fourfold increase in *M. pneumoniae* specific IgG when comparing acute phase and convalescent sera collected with an interval of 2–4 weeks. The need for a convalescent serum sample means the gold standard can only be established retrospectively and is not useful in clinical practice. Using only acute phase serology lacks both specificity and sensitivity. Specificity may be low because of the high prevalence of *M. pneumoniae*-specific IgM and IgG in healthy children, which has been reported to be up to 20% and 50%, respectively in healthy children over five years.[8] Sensitivity of serology to detect infectious diseases in general is known to be lower in the early phase of infection and in children under two years.[14] *M. pneumoniae* culture can take up to 2 to 6 weeks, requires special culture media containing sterols, is insensitive and therefore not available in many centers. *M. pneumoniae* PCR in upper respiratory tract specimens (e.g. pharyngeal swab, nasal washing) is fast and sensitive, but lacks specificity since neither PCR positivity nor high copy number discriminates asymptomatic carriage in the upper respiratory tract from lower respiratory tract infection.[8] Chest radiographs in *M. pneumoniae* pneumonia can show alveolar, interstitial as well as peribronchial infiltrates. Since radiographs do not reveal etiological agents, they are not routinely recommended in the diagnostic work-up of children with community-acquired pneumonia.[15] Concluding, there currently is no test that unequivocally distinguishes *M. pneumoniae* infection from carriage or from a previous *M. pneumoniae* infection. The clinician should attempt to combine patient characteristics and if needed order diagnostic tests whilst considering the limitations described above.

### Management

Treatment of *M. pneumoniae* RTI consists of supportive care and antibiotics. Due to the lack of a cell wall, *M. pneumoniae* are intrinsically insensitive to β-lactam antibiotics. Tetracyclines and fluoroquinolones are