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Mycoplasma pneumoniae infections — Does treatment help?

Emiel B.M. Spuesens [a,1], Patrick M. Meyer Sauteur [a,2], Cornelis Vink [a,b,3], Annemarie M.C. van Rossum [a,*]

[a] *Department of Pediatrics, Division of Infectious Diseases and Immunology, Erasmus University Medical Center-Sophia Children's Hospital, PO Box 2040, 3000 CA Rotterdam, The Netherlands*
[b] *Erasmus University College, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands*

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Summary *Mycoplasma pneumoniae* is a common cause of respiratory tract infections (RTI's), especially in children. While severe *M. pneumoniae* infections are generally treated with antibiotics, the diagnosis as well as treatment of these infections should be reconsidered in the light of recent clinical findings. First, *M. pneumoniae* was found to be carried in the upper respiratory tract of a relatively high percentage of healthy, asymptomatic children. Clearly, this complicates the diagnosis of a suspected *M. pneumoniae* RTI and, thus, the decision when to initiate treatment. A complication in the treatment of these infections is that data on the efficacy of antibiotic treatment of *M. pneumoniae* RTI's are sparse and derived exclusively from comparative studies. A recent Cochrane review concluded that there is insufficient evidence about the efficacy of antibiotics for *M. pneumoniae* lower respiratory tract infections (LRTI) in children. Due to side effects associated with the use of tetracyclines and quinolones in children, only macrolides can be used to treat *M. pneumoniae* infections in young patients. The general applicability of macrolides, however, is currently threatened by the worldwide increase in macrolide-resistant *M. pneumoniae* strains. Finally, limited evidence is available that corticosteroids might have an additional benefit in the treatment of *M. pneumoniae* infections. In this review, the current issues related to the diagnosis and treatment of *M. pneumoniae* infections will be discussed.

* Corresponding author. Tel.: +31 10 704 0704.
E-mail addresses: e.spuesens@erasmusmc.nl (E.B.M. Spuesens), p.meyersauteur@erasmusmc.nl (P.M. Meyer Sauteur), c.vink@erasmusmc.nl (C. Vink), a.vanrossum@erasmusmc.nl (A.M.C. van Rossum).
[1] Tel.: +31 10 704 0704.
[2] Tel.: +31 10 704 3951.
[3] Tel.: +31 61 214 0295.

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Introduction

Respiratory tract infections (RTI's) form a major burden of disease worldwide in children. The World Health Organization estimates that there are 150.7 million cases of pneumonia each year in children younger than 5 years of age, with as many as 20 million cases severe enough to warrant hospital admission.[1] A wide range of pathogens may cause respiratory tract infections. One of the most common bacterial causes of both upper and lower RTI is *Mycoplasma pneumoniae*. This bacterium is of particular importance in children, in which it is the second most common bacterial cause of pneumonia after *Streptococcus pneumoniae*.[2] In this review, we will focus on the treatment of RTI's caused by *M. pneumoniae* in children.

Biological characteristics of *M. pneumoniae*

M. pneumoniae is a human pathogen from the bacterial class of *Mollicutes* (lat. soft skin). The common features shared by the bacteria in this class are[1]: the permanent lack of a rigid cell wall,[2] relatively small cellular dimensions, and [3] a relatively small genome.[3–5] As a consequence of the limited genomic size, *M. pneumoniae* has a limited metabolic capacity; the bacterium is thus dependent on its host for the production of crucial biomolecules, such as purines and pyrimidines.[3] It is therefore imperative that *M. pneumoniae* be in close contact with its host to scavenge for nutrients. To establish a close association with the host respiratory epithelium, *M. pneumoniae* contains a specialized attachment organelle. This organelle consists of a number of adhesion proteins and accessory proteins that are essential for attachment.[6–8] Loss of function of one of these proteins results in a non-virulent bacterium that is unable to attach to the human respiratory epithelium.[9,10]

Diagnosis of *M. pneumoniae*

The clinical signs and symptoms of a *M. pneumoniae* RTI and available diagnostic assays have recently been reviewed elsewhere.[11] In short, there are no clinical, biochemical or radiological findings that are pathognomonic or specific for an *M. pneumoniae* RTI. Although a clinical syndrome has previously been described that was considered to be characteristic for *M. pneumoniae* infections (i.e. 'walking pneumonia'), a recent Cochrane review did not reveal any *M. pneumoniae*-specific clinical symptoms and signs.[12] The diagnosis of an *M. pneumoniae* RTI therefore has to be supported by microbiological findings. At present, different diagnostic techniques are available, but all of these have drawbacks that should be taken into consideration before starting treatment for a presumed *M. pneumoniae* RTI.

Although culture media have been optimized over the years, bacterial culture is still an insensitive tool to detect *M. pneumoniae* in clinical samples. In addition, it has a long turnaround time and is both laborious and expensive. The culturing of *M. pneumoniae* is therefore rarely used as a diagnostic method for clinical purposes. The current diagnosis of *M. pneumoniae* RTI relies either on the detection of serum antibodies against *M. pneumoniae* (serology) or on the detection of bacterial DNA in samples from the upper respiratory tract, as recommended in the guidelines published by the British Thoracic Society and the Infectious Disease Society of America.[13,14]

From a clinical point of view, serology is an inconvenient diagnostic tool since it requires a serum sample in the acute phase of the disease and a convalescent serum sample taken 2–4 weeks later to provide reliable results. This inherent retrospective aspect of serology is not helpful for clinicians to make a therapeutic management decision in the acute phase of the infection. As a consequence, clinicians often rely on single-sample IgM and IgG antibody titers in order to diagnose acute *M. pneumoniae* infections. Such a procedure, however, lacks predictive power. This was recently demonstrated in a study performed in the Netherlands, in which a similar range of single-sample *M. pneumoniae* IgM and IgG antibody titers was found in children with and without symptoms of an RTI.[15]

In the past two decades, a solution to the drawbacks of culture and serology has seemingly been provided by molecular diagnostic methods (based on nucleic acid amplification techniques, such as PCR), which can provide fast, sensitive, and specific results in the acute phase of an infection. Consequently, molecular methods are increasingly used in clinical practice, as well as in clinical studies for the detection of *M. pneumoniae* DNA. However, the above mentioned observational study on a population of children with and without signs of an RTI detected a similar prevalence of *M. pneumoniae* by real-time PCR in asymptomatic children and symptomatic children with 21.2% [95% CI 17.2%–25.2%] versus 16.2% [95% CI 12.2%–20.2%], respectively.[15] A difference in *M. pneumoniae* genomic copy load in respiratory tract samples was not detected between the symptomatic and asymptomatic group. Real-time PCR therefore does not represent an unambiguous method for the diagnosis of symptomatic *M. pneumoniae* infections. The diagnostic accuracy did not improve when the PCR results were combined with serological data.[15] Thus, at this moment, it appears that there is no definitive procedure that allows the reliable diagnosis of acute (symptomatic) infections with *M. pneumoniae*. Clearly, this notion has major consequences for the management of children with a symptomatic RTI and calls for novel procedures that allow discrimination between (harmless) carriage of *M. pneumoniae* and symptomatic infections caused by this bacterium.

Treatment of *M. pneumoniae* respiratory tract infections

Choice of antibiotics based on biological characteristics

M. pneumoniae lacks a rigid bacterial cell wall, but is instead protected by a sterol-containing membrane. As a direct result, *M. pneumoniae* has an innate resistance to any antibiotic that is directed at the destruction or disruption of a bacterial cell wall, such as beta-lactams and glycopeptides. In contrast, antibiotics that are directed at the inhibition of DNA metabolism and protein synthesis do