# Lower respiratory tract infections in adults : a clinical diagnostic study in general practice

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# Chapter VII

# Diagnosing *Mycoplasma pneumoniae* in general practice

***Diagnosing Mycoplasma pneumoniae in general practice***

## 7.1 Abstract

*Introduction*
*Mycoplasma pneumoniae* is one of the pathogens, which fairly frequently causes lower respiratory tract infections. Because of treatment consequences it would be desirable to identify this pathogen. In the present study we investigated the feasibility of discriminating between *Mycoplasma pneumoniae* (detected by real-time PCR) and other causes of lower respiratory tract infections on clinical grounds in adult patients in general practice.

*Methods*
From November 1998 until June 2001, patients aged ≥ 18 years were examined in a prospective observational study in general practices in the region of Leiden, The Netherlands. A standard medical history was taken and physical examination was performed. Sputum, blood and throat swabs were collected for diagnostic tests. According to findings by real-time PCR test, patients were classified into patients with and without *Mycoplasma* pneumoniae infection. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated.

*Results*
In twelve patients (11%) *Mycoplasma pneumoniae* was detected by real-time PCR. *Mycoplasma pneumoniae* was associated with the presence of a lower means age (OR 0.96, 95% CI 0.9-1.0), chills (OR 5.4, 95% CI 1.1-26.2), elevated ESR above reference value (calculation of OR was not possible for statistical reason), CRP>50mg/l (OR 5.1, 95% CI 1.1-24.7) and the absence of rhinitis (OR 0.1, 95% CI 0.0-0.5).

*Conclusions*
Although we found a lower mean age in patients with a *Mycoplasma pneumoniae* infection, the present study did not confirm it is a disease of only younger adults. Based only on clinical information differentiation between *Mycoplasma pneumoniae* and other pathogens in patients with LRTI is difficult. Because of therapeutic consequences, there is a need for a rapid diagnostic test, which can be used in general practice.

## 7.2 Introduction

The prevalence of *Mycoplasma pneumoniae* found in adult patients with Lower Respiratory Tract Infections (LRTIs) differs between studies. Recently performed studies showed values from 1% to 24%, depending on the population studied and the diagnostic methods used.[1,2] In adult patients consulting their general practitioner with LRTI we found 9% *Mycoplasma pneumoniae*, 9% *Haemophilus influenzae* and 6% *Streptococcus pneumoniae*.[3] *Mycoplasma pneumoniae* is known to cause epidemics in the open population at about 5 year intervals and may also cause outbreaks in institutions such as military bases.[4] This pathogen does not have a pepticloglycan cell wall and therefore is not susceptible to β-lactam antibiotics, which are often recommended when empirical treatment for LRTI is started, because they are an effective treatment for *Streptococcus pneumoniae* and *Haemophilus influenzae*.[4] *Mycoplasma pneumoniae* is susceptible to antibiotics, which interfere with protein synthesis for instance tetracyclines and macrolides.[4] On the other hand, tetracyclines and macrolides are not first choice of therapy for *Streptococcus pneumoniae* and *Haemophilus influenzae,* because of increased resistance of *Streptococcus pneumoniae* against these antibiotics.[5,6,7] Differentiation between the various pathogens that can cause LRTI is helpful for optimisation of antimicrobial treatment. For a general practitioner without additional facilities this differentiation should preferably be based on information that can simply be obtained from the medical history and physical examination. Several investigators used clinical information for the prediction of pathogens in patients with LRTI.[8,9] Farr et al.[8] , who investigated patients with community-acquired pneumonia at admission to hospital, found that an infection with *Mycoplasma pneumoniae* was related to a lower age compared to patients without a *Mycoplasma pneumoniae* infection. Dorigo-Zetsma et al.[9] found that the absence of coryza was correlated with the presence of *Mycoplasma pneumoniae* in children with respiratory tract infection compared to other or unknown aetiology. A study by Macfarlane et al.[10] did not find a relation between chest radiographic features and *Mycoplasma pneumoniae.* Serological methods are not useful to detect pathogens in the acute phase of a disease; since these methods take at least two weeks (second sample in convalescent phase).[11] This is not the case for molecular diagnostic methods. Recently a real-time polymerase chain reaction (PCR) assay for rapid detection of *Mycoplasma pneumoniae* on throat swabs has become available.[11]
In the present study we investigated the feasibility of discriminating between *Mycoplasma pneumoniae* (detected by real-time PCR) and other causes of lower respiratory tract infections on clinical grounds in adult patients in general practice.

## 7.3 Methods

Adult patients aged 18 and over, consulting their general practitioner (GP) for LRTI in the Leiden region, The Netherlands, were included between November 15, 1998 and June 1, 2001. The definition of LRTI used for the inclusion of patients is: (1) any abnormality on pulmonary auscultation and (2) at least two of the following three signs and symptoms; (a) fever >38°C, or fever in the past 48 hours (reported by patient); (b) dyspnoea or cough (productive or non-productive); (c) tachypnoea, malaise or confusion. Patients who were pregnant or had diseases that could have obstructed completion of follow-up were excluded. A standard medical history and physical examination was done. Sputum samples, throat swabs and blood samples were collected for microbiological analysis. Detailed information on case-definition, patients, investigations done and aetiology were described in chapter 3. The real-time PCR assay was described in detail elsewhere.[9]
Data were analysed using SPSS version 11.0 for Windows. The chi-square test was used to compare percentages between groups. The significance level was set at 0.05. The Student T-test was used to compare means in continues variables and in case of a skewed distribution the Mann-Whitney test was used. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

## 7.4 Results

During the study period 145 patients were included. A complete set of samples was available for 106 patients (sputum, throat swabs and blood samples). Out of these 106 in 12 patients *Mycoplasma pneumoniae* was detected by real-time PCR. All positive real-time PCR tests were affirmed by serology. Two-third of the patients with a *Mycoplasma pneumoniae* infection were men. The patients with a *Mycoplasma pneumoniae* infection had a lower mean age (43 years) compared to patients without (51 years) *Mycoplasma pneumoniae* (P-value <0.05). Most patients with *Mycoplasma pneumoniae* (n=8) were seen in the age group 41-50 years. Only two patients with a *Mycoplasma pneumoniae* infection were older than 50 years. The clinical features of patients with a positive *Mycoplasma pneumoniae* PCR-test compared to patients with a negative test are given in table 7.1. A positive test was associated more frequently with the presence of chills, and the detection of elevated ESR (above reference value, adjusted for age and sex) or CRP (>50 mg/l) levels. Rhinitis was more often seen in patients with a negative test. Fever as reported by the patient was present in all patients with *Mycoplasma pneumoniae,* but we found fever on first examination in only 6 of the 12 patients.

**Table 7.1 The comparison of clinical features between patients with positive real-time PCR test for *Mycoplasma pneumoniae* and patients with negative test**

| | *M. pneumoniae* positive n=12 (%) | *M. pneumoniae* negative n=94 (%) | P-value | Crude OR[a] (95%,CI)[b] |
|---|---|---|---|---|
| Sex (number of woman) | 4 (33) | 52 (55) | 0.15 | 0.4 (0.1-1.4) |
| Age, mean years | 43 (SD9) | 51 (SD 16) | **<0.05** | **0.96 (0.9-1.0)** |
| Ex- or current Smokers | 6 (50) | 58 (62) | 0.54 | 0.6 (0.2-2.1) |
| Co-morbidity | 3 (25) | 45 (48) | 0.13 | 0.4 (0.1-1.4) |
| Acute onset | 3 (25) | 23 (25) | 1.00 | 1.0 (0.3-4.1) |
| Fever [d] | 12 (100) | 77 (82) | 0.21 | [c] |
| Rhinitis | 1 (8) | 58 (62) | **<0.001** | **0.1 (0.0-0.5)** |
| Hoarse voice | 5 (42) | 34 (36) | 0.76 | 1.2 (0.4-4.3) |
| Chills | 10 (83) | 45 (48) | **0.02** | **5.4 (1.1-26.2)** |
| Sore throat | 5 (42) | 37 (39) | 1.00 | 1.1 (0.3-3.7) |
| Headache | 9 (75) | 76 (81) | 0.70 | 0.7 (0.2-2.9) |
| Myalgia | 8 (67) | 62 (66) | 1.00 | 1.0 (0.3-3.7) |
| Nausea | 6 (50) | 39 (42) | 0.57 | 1.4 (0.4-4.7) |
| Diarrhoea | 1 (8) | 26 (28) | 0.29 | 0.2 (0.03-1.9) |
| Chest pain, retro sternal | 5 (42) | 21 (22) | 0.16 | 2.5 (0.7-8.6) |
| Chest pain, on breathing | 1 (8) | 30 (32) | 0.17 | 0.2 (0.02-1.6) |
| Short of breath | 8 (67) | 72 (77) | 0.45 | 0.6 (0.2-2.2) |
| Sputum production | 7 (58) | 77 (82) | 0.12 | 0.3 (0.1-1.1) |
| Yellow/green sputum | 6 (50) | 40 (43) | 0.62 | 1.4 (0.4-4.5) |
| Tachypnoea (>16/min) | 10 (83) | 72 (77) | 0.73 | 1.5 (0.3-7.5) |
| Pulse (>100/min) | 1 (9) | 4 (5) | 0.45 | 2.1 (0.2-20.7) |
| Temperature (≥38°C)[e] | 6 (50) | 37 (39) | 0.54 | 1.5 (0.5-5.1) |
| Seriously ill | 5 (42) | 17 (18) | 0.12 | 3.2 (0.9-11.0) |
| Painful lymph nodes | 0 (0) | 9 (10) | 0.59 | [c] |
| Intercostal retractions | 1 (8) | 17 (18) | 0.69 | 0.4 (0.1-3.4) |
| Dullness on percussion | 1 (8) | 20 (21) | 0.45 | 0.3 (0.04-2.8) |
| Diminished breath sounds | 1 (8) | 14 (15) | 1.00 | 0.5 (0.1-4.3) |
| Rhonchi | 8 (67) | 62 (66) | 1.00 | 1.0 (0.3-3.7) |
| Crepitations | 5 (42) | 48 (51) | 0.54 | 0.7 (0.2-2.3) |
| Infiltrate chest X-ray | 4 (33) | 16 (18) | 0.25 | 2.3 (0.6-8.4) |
| CRP>20 mg/l (n=101) | 11 (92) | 64 (72) | 0.18 | 4.3 (0.5-35.0) |
| CRP>50 mg/l (n=101) | 10 (83) | 44 (49) | **0.03** | **5.1 (1.1-24.7)** |
| ESR elevated[f] (n=102) | 12 (100) | 52 (58) | **0.003** | [c] |

*[a] OR=odds ratio. [b] CI=Confidence interval. [c] Calculation of OR not possible for statistical reason. [d] Fever as reported by patient. [e] Temperature as measured at first visit. [f] Number of patients with ESR above reference value (The ESR normal levels were adjusted for age and sex as follows: for females of age 18 to 51 years, the normal level was 0 to 25 mm/h; for females of age 51 to 66 years, the normal level was 0 to 30; for males of age 18 to 51 years , the normal level was 0 to 15; for males of age 51 to 66 years, the normal level was 0 to 20; for males and females of more than 66 years of age, the normal level was 0 to 40).*

## 7.5 Discussion

In the present study a positive test result for *Mycoplasma pneumoniae* was seen in 12 of the 106 patients with lower respiratory tract infection of whom a real-time PCR was available, which was associated with a lower mean age, the absence of rhinitis, the presence of chills and elevated blood tests for ESR or CRP. Though patients with a positive test for *Mycoplasma pneumoniae* had a relative lower mean age, the majority of patients was between 40 and 50. This means that *Mycoplasma pneumoniae* can also cause LRTI in patients of middle age. A lower mean age in adult patients with a *Mycoplasma pneumoniae* infection was also found by Farr et al.[8] in 73 patients out of 441 patients admitted to hospital for pneumonia (confirmed by chest X-ray) compared to patients with *Streptococcus pneumnoniae* or patients with unknown origin and by Beović et al.[12], who investigated 113 patients with pneumonia on chest X-ray and compared the mean age of 22 patients with *Mycoplasma pneumoniae* to patients with *Streptococcus pneumnoniae* or *Chlamydia pneumnoniae.* A study by Dorigo-Zetsma for the frequency of *Mycoplasma pneumoniae* infection among patients with acute respiratory infection showed that the rates of *Mycoplasma pneumoniae* in different age groups were comparable (between 2 and 6%) including children (22% of the included patients were children between 0-15 years of age).[13] This study did not use a case-definition for acute respiratory infection. The high frequency of chills and high levels of CRP in blood samples, which we found in patients with *Mycoplasma pneumoniae* were also found by Beović et al.[12] The finding of the absence of rhinitis as feature, which was associated with *Mycoplasma pneumoniae*, also was found in a study in children by Dorigo et al.[8]

We tested the association between the presence of *Mycoplasma pneumoniae* and a rather large number (>30) of variables, which means that there is a possibility that some variables could be significant by change. Therefore the results should be taken with caution. The number of 12 patients with a *Mycoplasma pneumoniae* infection is too low to draw firm conclusions and therefore we did not perform multivariate regression analysis.

In the analysis we compared patients with a positive test for *Mycoplasma pneumoniae* with patients with a negative tests result for *Mycoplasma pneumoniae*, which is close to every day practice when patients who need a different treatment have to be discriminated from all other patients with LRTI.

To determine if the differences in mean age between patients with *Mycoplasma pneumoniae* and patients without *Mycoplasma pneumoniae* could be caused by factors due to the general practitioner's, we have performed stratified analysis. We observed that patients in whom *Mycoplasma pneumoniae* was detected came from 6 GPs who included 57% of the patients in the study. It could have been that these GPs tended easily to ask patients for the study and that these GPs therefore have selected a different population of patients, i.e. a younger

population. For these GPs, the mean age of the referred patients without *Mycoplasma pneumoniae* (50 years), was not significantly different from the mean age (53 years) of patients included by GPs who turned out not to have include patients with *Mycoplasma pneumoniae*. This means that this mean difference in age cannot be attributed to confounding by general practitioner-related factors.
In our diagnostic rule, which we developed for the presence of a bacterial infection (chapter 6) fever, headache and painful cervical lymph nodes were positively associated and rhinitis and diarrhoea were negatively associated with a bacterial infection.[14] From these variables rhinitis was also negatively associated with *Mycoplasma pneumoniae.* The 12 patients with *Mycoplasma pneumoniae* are also part of the diagnostic rule for a bacterial infection, which makes it difficult to compare the variables related with bacterial infection to the variables related with *Mycoplasma pneumoniae*. Our impression, although based on a small number of *Mycoplasma pneumoniae* infections, that it is difficult to diagnose *Mycoplasma pneumoniae* only with the use of medical history taking and physical examination was also seen by Beović et al.[12], who found a substantial overlap in clinical features in patients with pneumonia caused by different pathogens.
In conclusion, although we found a lower mean age in patients with a *Mycoplasma pneumoniae* infection, the present study did not confirm it is a disease of only younger adults.
The fact that it is difficult, if not impossible, to differentiate on clinical grounds between *Mycoplasma pneumoniae*, *Haemophilus influenzae* and *Streptococcus pneumoniae*, which are the most frequently found bacterial pathogens in patients with LRTI and the fact that these pathogens have different first choice of therapy has consequences for the treatment of LRTI in general practice. The need for a rapid test, which can be used in general practice to diagnose *Mycoplasma pneumoniae* is obvious. The treatment problems, which general practitioners meet in the management of patients with LRTI are discussed in chapter 8.

## 7.6 References

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