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Respiratory tract infections by *Mycoplasma pneumoniae* in children: a review of diagnostic and therapeutic measures

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Abstract This review discusses the current knowledge on laboratory tests and treatment of respiratory tract infections caused by *Mycoplasma pneumoniae* (MP) in children. MP infection is endemic in most areas of the world. The highest incidence is seen in children aged between 3 and 14 years. Most infections are mild and non-pneumonic. Parapneumonic complications of MP pneumonia are rare. Complications are described affecting the skin, central nervous system, kidneys, heart, muscles and the eyes. To diagnose an acute MP infection in children, a combination of PCR and IgM serology is sensitive and convenient. In both tests it is possible to obtain a result in 1 to 2 days. As a consequence, adequate antibiotic treatment can be prescribed to the child. Macrolides are the first choice in treatment of MP infection in children.

Conclusion The most sensitive and rapid test to diagnose a *Mycoplasma pneumoniae* infection in children is a combination of nasopharyngeal polymerase chain reaction and IgM enzyme immunoassay. The treatment of choice in children is a macrolide.

Key words Laboratory diagnosis · *Mycoplasma pneumoniae* · Outcome · Review · Therapy

Abbreviations *CFA* complement fixation assay · *EIA* enzyme immunoassay · *ELISA* enzyme-linked immunosorbent assay · *MP Mycoplasma pneumoniae* · *PCR* polymerase chain reaction

Introduction

Some 16 *Mycoplasma* species are found in humans [126]. These species, belonging to the class of *Mollicutes*, may colonise the oropharynx and genitourinary tract of humans. Several *Mycoplasma* species including *Mycoplasma salivarium*, *Mycoplasma orale*, *Mycoplasma buccale*, *Mycoplasma faucium* and *Mycoplasma lipophilum* are part of the normal flora of the human oropharynx, but only *Mycoplasma pneumoniae* (MP) may be encountered as a pathogen. Of the infections caused by MP, roughly 20% are asymptomatic, the majority (±75%) are minor respiratory illnesses (tracheobronchitis, pharyngitis etc.) and only a small proportion (3–10%) are serious infections such as pneumonia [16,29]. In children, MP accounts for 10–40% of all cases of community-acquired pneumonia, which is influenced by epidemics [26, 28, 29, 43, 45, 110].

Here an overview of respiratory tract infections caused by MP in children is provided with a special focus on laboratory tests and treatment.

Epidemiology

Infection due to MP is endemic in most areas of the world, although it is more common in temperate zones. Infection occurs during all months of the year, but is slightly more frequent during late summer and early

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autumn [121]. The incidence of MP infections varies every year with an epidemic peak approximately once every 4 years [29, 55, 90]. Hauksdottir et al. [55] showed that outbreaks of MP were similar in timing and pattern in different countries in Europe.

The prevalence of infection of all clinical syndromes caused by MP varies from 2% during endemic years to 10–35% in epidemic periods [15, 42, 84]. The highest incidence is seen in children aged between 3 and 14 years. Another peak in the age distribution is found in adults between 25 and 40 years. In the youngest group, boys predominate and there is no explanation for this difference in gender distribution. In the second age peak, women predominate [88]. The rate of MP infections under endemic conditions in children aged 5–9 years was 4/1000 per year and in children between 10 and 14 years 3/1000 per year [15, 42]. Due to the long incubation period (2–3 weeks) and low transmission rate, the duration of the epidemic lasts approximately 1 year. Spread of infection from person to person is very slow, therefore one may deduce that very close contact is needed. MP is transmitted by direct contact or by contaminated respiratory droplets. Foy et al. [41] reported that it took several months before infection by MP was disseminated among four households. Spread among playmates in the neighbourhood seemed more important than that in the classroom.

MP has the propensity to cause very intensive outbreaks in facilities where people live in very close contact. In the late 1960s, outbreaks in military institutions, universities, homes for mentally disabled or homes for psychiatric patients were reported [14, 22, 36, 100, 113, 119]. More recently Feikin et al. [38] reported an outbreak of MP in combination with adenovirus at a Federal Service Training Academy. Of a group of 586 students, 54% reported respiratory illness during the outbreak period. The outbreak showed peaks of illness every 2–3 weeks.

MP infection is rarely diagnosed under the age of 6 months. Several explanations can be given: protection by maternal antibodies and/or immaturity of receptors for MP in the respiratory tract, or this agent is rarely considered in infants [15, 131]. MP may cause up to 35% of all cases of outpatient pneumonia and 3–18% of pneumonia cases necessitating hospitalisation [91]. Recurrent infection by MP is not uncommon. In people with pre-existing immunity against MP re-infection may occur after a lapse of 3 to 5 years [46]. Second episodes appear to be milder. Re-infection is less commonly seen after pneumonia than after infection with minor symptoms [43]. This might be explained by elevated complement-fixing antibodies measurable for 2 to 9 years after pneumonia. These antibodies, however, fall very rapidly after the 2nd year in persons with mild upper respiratory tract infections [43].

Clinical manifestations

In children younger than 5 years of age, MP infections are mostly mild and non-pneumonic. The major symptoms are coryza and wheezing without concurrent fever. In children between 5 and 15 years of age, the risk for MP-induced pneumonia is maximal. More than 30% of infections caused by MP in this age group result in pneumonia [121].

MP infection is a subacute and gradual process. Illness usually lasts for 1 month or longer, excluding the incubation period [29]. Clinical symptoms normally start in the upper respiratory tract and then spread to the lower respiratory tract. The initial manifestation is usually a sore throat followed by hoarseness or dysphonia [91]. When the infection reaches the trachea, bronchi and bronchioles, an intractable cough appears. It is a constant, relatively nonproductive cough that keeps the patient awake. When the disease progresses, fever becomes higher, the cough more troublesome and the patient may become dyspnoic [91]. Table 1 summarises the symptoms and signs of lower respiratory MP infection from three studies. Stevens et al. [120] studied 44 children ranging from 16 months to 14 years. The other two investigators compiled their data from different studies in children and adults [24, 29]. Stevens et al. [120] reported that in their group coryza was more commonly seen in the younger children. Headache and production of sputum in association with MP pneumonia varies between studies [24]. This is probably caused by the difference in ages of the patients between the studies.

Severe illness may be seen in the presence of a concomitant infection [56, 91, 118]. Heiskanen et al. [56] reported that in 50% of the patients infected with MP, another aetiological agent was involved. Hers et al. [58] found co-infection with *Haemophilus influenzae* in 6% of the patients infected with MP. Block et al. [13] reported co-infection of MP and *Chlamydia pneumoniae* in 8% of community-acquired pneumonia. Severe manifestations can be seen in patients with sickle cell disease, Down syndrome, immunodeficiency syndromes, drug-induced immunosuppression and pre-existing cardiopulmonary dysfunction [15, 91].

Pneumonia

On physical examination rales and rhonchi are common, but signs of consolidation are seldom detected. On the chest radiograph MP pneumonia appears mostly diffuse and with reticular infiltrates, consolidation is infrequent. In 20% of cases, bilateral abnormalities are seen. Cough, abnormal chest signs, and radiographic changes may last several weeks. Pleuritic chest pain and pleural effusion are unusual [121].

Severe pneumonia may be due to an enhanced host cellular immune response [21]. This may lead to bronchiolitis obliterans, based on the obstruction of the terminal and respiratory bronchioles by polypoid/fibroblastic masses. Recently, bronchitis obliterans was described by Leong et al. [86] with involvement of the larger bronchi. Kim et al. [75] evaluated children who

Table 1 Symptoms and signs (given as percentage) in lower respiratory tract MP infection

Symptom	Reference		
	[120][a]	[24][b]	[29][c]
Cough	98	100	93–100
Malaise	86	75	74–89
Nasal discharge and/or sore throat	59	25[d]	29–71
Vomiting	39	25	
Abdominal or chest pain	34	25[e]	42–69[e]
Headache	32	50	60–84
Production of sputum	27	50	
Skin rash	20		
Fever >38 °C	59	100	96–100
Crepitations	59		
Pharyngitis	32	50	12–73
Rhonchi	32		
Bronchial breathing	27		
Otitis media	27	10	
Rales		75	80–84

[a] Study in 44 children
[b] Compilation of eight studies in children and adults
[c] Compilation of four studies
[d] Only sore throat
[e] Only chest pain

had MP pneumonia 1 to 2 years after active disease with high-resolution computed tomography. Of these patients, 37% had pulmonary sequelae. The site of the sequelae corresponded with the site of pneumonia on the chest radiograph at the time of infection. Mosaic perfusion was the most frequent finding. Marc et al. [94] evaluated pulmonary function in children 6 months and 1 year after MP pneumonia. Of these patients, 50% had abnormal pulmonary gaseous diffusion measured by diffusion of carbon monoxide. No change in lung flow or volume was found. The decrease in carbon monoxide diffusion was associated with delay to start macrolide treatment and a short duration of this treatment.

Parapneumonic complications of MP pneumonia in children are rare. However, in the literature various complications are described in the skin (Stevens-Johnson syndrome) [87], the central nervous system [81, 123], kidneys [111, 129], heart [23, 97], muscles [10] and the eyes [98]. The pathophysiology of extrapulmonary manifestations of MP is not understood. It has been suggested that toxins or auto-antibodies play a role [27, 39, 76, 80, 89]. Direct invasion of MP of the organs is another possibility.

In Stevens-Johnson syndrome as a complication of MP, 80% of the patients present with upper respiratory tract symptoms. However, 60% of these patients had abnormalities on a chest radiograph [87]. The exanthem is predominantly maculopapular and vesicular. The distribution of the exanthem is mainly on the trunk and extremities. The incidence of the Stevens-Johnson syndrome associated with MP is about 1–5% [4, 87]. The incidence of central nervous system manifestations associated with MP infection is only 0.1%. In 38% of these patients there is also involvement of the respiratory tract. In children, encephalitis is the most frequent presentation [81]. Recently, Papaevangelou et al. [105] reported Bell palsy associated with MP pneumonia. Stroke, Guillain-Barré syndrome and acute transverse myelitis are also rare complications of MP infection [44, 57, 99]. Glomerulonephritis is occasionally seen as a complication of MP pneumonia in children. Said et al. [111] described 24 patients with proliferative glomerulonephritis and MP infection of whom 6 were children with pneumonitis. The prognosis regarding the acute renal failure seems to be good. Carditis is considered a very rare complication. In children, myocarditis, pericarditis and perimyocarditis have been reported. Carditis associated with MP is a serious disease leading to sequelae in 50% of the patients [97]. Berger and Wadowksy [10] described a 15-year-old girl with massive rhabdomyolysis associated with a MP infection [1]. The authors stated that perhaps polymerase chain reaction (PCR) analysis of throat swabs of patients with idiopathic rhabdomyolysis will lead to a better understanding of the association between MP and rhabdomyolysis. Opthalmological manifestations are uncommon, except for conjunctivitis. In some cases the presentation of papillitis leading to iritis or oculomotor nerve palsy has been described [98].

Laboratory diagnosis

Culture

Nowadays with the availability of rapid tests by PCR and enzyme immunoassays, culture is an invalid method for the detection of MP. MP is a fastidious agent and culture of MP is insensitive, time consuming and has no influence on treatment [6, 54, 73, 115]. In the past, culture was used as a reference to evaluate new methods. From a clinical point of view, culture is of little value [1, 54, 64, 74, 92].

Antigen detection

Enzyme immunoassays (EIA) used directly on nasopharyngeal aspirates form a rapid and specific test for MP detection [59, 60, 77, 78]. Detection limits range from 10^3–10^5 colony forming units/ml. With the increasing availability of PCR techniques, EIA on nasopharyngeal aspirates is being less used. However, in the early phase of the infection this technique can be used as an alternative to PCR (or culture) or an addition to serology.

Polymerase chain reaction

Over the last decade PCR for MP has been developed. In 1989, Bernet et al. [11] and Jensen et al. [68] showed in animals and simulated clinical samples that it was possible to detect specific DNA sequences of MP. In 1992,

Skakni et al. [116] were the first to evaluate the use of PCR to detect MP in clinical samples (bronchoalveolar lavages or nasopharyngeal aspirates) in children. Efforts have been made to develop the PCR test for routine use.

The first target sequence used was a 144 bp sequence specific for MP from a genomic library developed by Bernet et al. [11]. Over the years other target sequences have been investigated: the P1 virulence gene [19, 31, 68, 132] the 16S rRNA gene [69, 112, 124, 128] and the elongation factor gene [92]. All these primers are still used. In 1995 Buck and Eid [17] introduced a more simple PCR method for detection of MP in throat swabs from children. Others also modified the procedure [1, 64]. This resulted in a replacement of the phenol-chloroform extraction by treatment with proteinase K, freezing/boiling of the specimen prior to the amplification, no hybridisation step and visual inspection of the gel. Recently, Honda et al. [62] described a capillary PCR in which the rate of heat conduction is improved leading to shortened reaction times. Hardegger et al. [51] described a real-time PCR assay: the 5′–3′ nuclease activity of Taq DNA polymerase is used to digest the probe which hybridises to part of the target DNA amplified by PCR. After cleavage of the probe which correlates with amplicon formation, a fluorescence signal is released. There is no need for gel detection, which makes this method rapid. The overall agreement between this method and a semi-nested 16S rDNA PCR was 97.4%. The development of multiplex PCR techniques including different micro-organisms (e.g. MP, *Chlamydia pneumoniae*) is a promising technique for the diagnosis of lower respiratory tract infections in children [30, 49].

The sensitivity and specificity of different PCR protocols for detection of MP ranges from 78% to 92% and 92% to 100%, respectively [12, 32, 64, 92, 103]. Comparison of the protocols is difficult because of differences in sample collection (throat swab, nasopharyngeal aspirate), preparation of the sample and procedures of amplication. Because of the lack of a ''gold standard'', PCR tests are compared to different reference methods. Ieven et al. [64] found PCR inhibitors in 26% of undiluted nasopharyngeal aspirates. This was earlier described by Reznikov et al. [109] who found 36% inhibitors in nasopharyngeal aspirates and not in throat swabs. However, the high specificity and sensitivity confirm that PCR is a good method for the detection of MP. It is also a rapid test allowing the diagnosis to be made in 1 to 2 days. This is important because MP pneumonia cannot be clinically differentiated from pneumonia caused by other pathogens. On basis of the result of the rapid PCR test an adequate choice can be made for the antibiotic treatment of a child with MP infection.

Serology

These techniques are based on the detection of antibodies of the different classes. As MP infection is a gradual process at the time of clinical presentation, antibodies are usually already detectable. IgM antibodies appear 7 to 10 days after infection. IgG antibodies are not present in the acute phase of infection but appear around 3 weeks after infection.

Complement fixation assay

The complement fixation assay (CFA) is routinely used for the serodiagnosis of MP infection [6, 34, 66]. The antigen used in the CFA is a chloroform-methanol glycolipid extract of MP cells. The CFA test measures predominantly IgM antibodies and to a minor extent IgG antibodies. A fourfold or greater titre rise in paired sera or a titre of ≥1:32 in a single serum sample is considered as a positive test. In a 12-year study, the sensitivity and specificity were 90% and 94%, respectively, when compared to culture [73]. In a recent study with sera from patients during suspected outbreaks of respiratory infections caused by MP, CFA was used as the gold standard. In the acute phase, 38% of serum samples were positive, but in combination with convalescent phase serum, 95% of the samples were positive [122]. CFA does not discriminate in the acute phase whether MP is involved, but with paired sera for epidemiological studies or evaluation of new tests, it can be a useful tool. CFA is time-consuming (requires 2 days), laborious, has a low specificity and has a lower sensitivity than immunofluorescence and enzyme linked immunosorbent assay (ELISA) [9, 67, 79, 102, 107, 115]. False-positive results with CFA based on cross-reactivity with antigens in *Streptococcus MG* and *Staphylococcus aureus* have been reported [40].

Enzyme-linked immunosorbent assay, enzyme immunoassay and immunofluorescence assay

These labelled-antibody techniques have fairly similar general principles and are discussed together. In ELISA and EIA, the anti-human immunoglobulin is labelled with an enzyme, in immunofluorescence assays, the anti-human immunoglobulin is directly labelled with a fluorochrome.

In the early 1980s, the first ELISA techniques were performed with whole-cell antigen preparations [18, 35, 108, 127]. As this technique developed, membrane proteins were introduced as antigens [26, 34, 63, 67]. Many commercial assays for routine diagnostics were developed and compared to CFA tests. The sensitivity and specificity range from 71% to 92% and 80% to 98%, respectively [2, 8, 25, 37, 40, 61, 85]. These tests are difficult to compare because of different tests formats. Thacker et al. [122] recently compared three commercial EIAs: the Meridian IC EIA, the Remel EIA and the ImmunoWELL-IgM EIA. All sera were also tested with a CFA. The Meridian IC EIA and ImmunoWELL-IgM EIA detected IgM only; the other two tests detected IgM and IgG. The Meridian IC EIA was most sensitive for

early detection of IgM, 47% of the sera from patients during suspected outbreaks of respiratory infections caused by MP were IgM positive in the acute phase serum. The paired sera showed positivity in 95% by CFA, 94% by Remel EIA, 81% by Meridian IC EIA and 45% by ImmunoWELL-IgM EIA. The detection of IgM alone is not useful for all cases of MP infection. Sillis et al. [115] reported that a primary MP infection and MP re-infection may be differentiated by the presence or absence of IgM in the presence of elevated specific IgA. Granstrom et al. [47] agreed that detection of IgA is valuable for the early diagnosis of MP infection. They concluded that detection of all three classes of immunoglobulins are needed for an optimal serodiagnosis.

To diagnose an acute MP infection in children, a combination of PCR and IgM serology is sensitive and convenient [32, 128, 130]. Waris et al. [130] concluded that with a combination of PCR in nasopharyngeal aspirates with a IgM–capture immunoassay in acute-phase sera, the sensitivity of rapid laboratory diagnosis is increased to 95%. In the reconvalescent phase of the infection, IgG serology can be of additional value [122]. The advantage combining IgM serology and PCR is that in the early phase of the infection when the IgM antibodies are not yet present, PCR obviate this phase. In both tests, it is possible to obtain a result in 1 to 2 days. As a consequence, adequate antibiotic treatment can be prescribed. Table 2 shows the diagnostic tests for the detection of MP and the time taken until the results are available. A ranking in practical preference was made.

Treatment

MP infection is a self-limiting disease. In untreated MP infection the constitutional symptoms like fever, headache and malaise resolve in about 10 days. Manifestations like cough and rales resolve more slowly. Antibiotic treatment is believed to result in a reduction of the duration of the symptoms and signs. Furthermore, rapid start and adequate duration of treatment with an effective dose of a macrolide for 14 days might prevent abnormal pulmonary gaseous diffusion measured by diffusion of carbon monoxide [94].

As MP lacks a cell wall, it is not susceptible to penicillins or other antibiotics acting on this structure. The bacteriostatic antibiotics tetracycline and macrolides are effective in the treatment of MP infection [4, 6, 96]. In children, macrolides are the first choice to treat MP infection because tetracyclines are contraindicated in children under the age of 8 years. Within the last 10 years, several new macrolide antibiotics have been studied in the treatment of MP infection.

In vitro susceptibility of macrolides to MP showed good results. MP isolates were susceptible to a clarithromycin concentration of 0.008 mg/l [20]. Ishida et al. [65] investigated the in vitro activity of azithromycin. This macrolide was the most potent macrolide against MP. For 90% of the tested strains, the minimal inhibitory concentration towards MP was 0.00024 μg/ml. Kaku et al. [71] found a minimal inhibitory concentration of roxithromycin against MP in the range of 0.0156–0.00625 mg/l. Comparative clinical trials were performed in which one macrolide was compared to the other. Since untreated controls were not included, the described success rates did not take spontaneous resolution into account. Cassell et al. [13] and Block et al. [20] compared clarithromycin with erythromycin in the treatment of MP infection. The clinical cure rate was 98%, the radiological success rate 98% and the eradication of MP was 100%. Schonwald et al. [114] and Manfredi et al. [93] compared the efficacy of azithromycin with erythromycin in atypical pneumonias and lower respiratory tract infections. The clinical cure rates were 100% and 96.1%, respectively. Harris et al. [53] studied safety and efficacy of azithromycin in children with community-acquired pneumonia compared to amoxicillin-clavulanate and erythromycin. The clinical cure rate after 15 to 19 days and 4 to 6 weeks was 100% with azithromycin treatment. Culture was done after 15 to 19 days in 14 children of the azithromycin group. All showed eradication of MP. In the comparative group, eradication was seen in four of six treated with erythromycin and persisted in the one child who was treated with amoxicillin-clavulanate. Kaku et al. [71] evaluated the clinical efficacy of roxithromycin in the treatment of MP pneumonia. The cure rate was 92.3%. Schonwald et al. [114] compared roxithromycin with azithromycin in the treatment of atypical pneumonia. The clinical cure rates were 94.3% and

Table 2 Diagnostic tests for the detection of MP infection. (*NPA* nasopharyngeal aspirate, *PS* pharyngeal swab)

Diagnostic test	Material	Sensitivity/Specificity	Time to result	Practical preference
Culture	NPA/PS	Not useful	Weeks	Not useful
EIA	NPA	Useful	1 Day	Useful
PCR	NPA/PS	Preferable	1 Day	Preferable
CFA				
Acute phase	Serum	Not useful	2 Days	Not useful
Convalescent phase	Serum	Preferable	Weeks	Useful[a]
EIA				
IgM/ acute phase	Serum	Preferable	1 Day	Preferable
IgM + G/ convalescent phase	Serum	Not useful	Weeks	Useful[a]

[a] For confirmation and epidemiology useful

98.9%, respectively. Currently, the newer macrolides are preferred over erythromycin because of their easy regimen and lesser side-effects [13, 20, 45, 48, 52, 82, 83, 93, 117]. Treatment regimens in children should be: clarithromycin in a dosage of 15 mg/kg per day divided in two doses for 10 days, azithromycin in a dosage of 10 mg/kg per day for those children with a body weight of ≤45 kg and 500 mg/day for those >45 kg for 3 days and roxithromycin in a dosage of 5 to 8 mg/kg per day divided in two doses for a maximum of 10 days [82, 83, 95].

New quinolones seem to be promising agents in the treatment of MP infection [7, 70, 72]. However, clinical trials with quinolones in children with community-acquired pneumonia have not yet been performed. Looking at the in vitro activities, grepafloxacin and gemifloxacin seem to be the most potent against MP [33, 50]. Both compounds had a in vitro minimal inhibitory concentration of 90% of the strains tested of 0.125 mg/l. In clinical trials in adults with community-acquired pneumonia treated with grepafloxacin, itshowed clinical success rates of 76% to 90% and eradication of 89% to 95% of the pathogens involved [101, 104, 125]. These studies also showed that it was well tolerated; however, grepafloxacin has been recently withdrawn because it caused ventricular tachycardia linked to excessive QT interval prolongation [5, 106]. The surplus value of the quinolones is the fact that they are bactericidal whereas the macrolides are bacteriostatic. However, the excellent success rates with macrolides and the potential for resistance development and side-effects when using quinolones reduce the necessity to use quinolones in children.

Summary

MP infection is endemic in most areas of the world. Annual rates of infection vary between 2% in endemic periods and 35% in epidemic periods. The highest incidence is seen in children between 3 and 14 years. MP may cause up to 35% of all cases of community-acquired pneumonia and 3–18% of pneumonia necessitating hospitalisation. MP infection is a subacute and gradual process. Clinical symptoms normally start in the upper respiratory tract and then spread to the lower respiratory tract. Parapneumonic complications of MP pneumonia in children are rare. The most sensitive and rapid tests to diagnose MP infection in children is a combination of nasopharyngeal PCR and IgM enzyme immunoassay. IgG serology has additional value in epidemiology. The treatment of choice for MP infection in children is a macrolide. Treatment is believed to diminish the duration of signs of symptoms.

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