Clinical characteristics of children with Mycoplasma pneumoniae infection hospitalized during the Danish 2010-2012 epidemic

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ABSTRACT

INTRODUCTION: *Mycoplasma pneumoniae* is a common cause of community-acquired pneumonia. Pneumonia may be the most severe manifestation of respiratory *M. pneumoniae* infection. The most typical symptoms in children are cough and wheezing, which are often accompanied by upper respiratory tract manifestations mimicking viral respiratory syndromes.

MATERIAL AND METHODS: This was a retrospective descriptive study. We included all children hospitalized at the Department of Paediatrics, Hvidovre Hospital, Denmark, from 1 August 2010 through May 2012 who tested positive for *M. pneumoniae* by polymerase chain reaction (PCR). Clinical data were obtained from the medical charts.

RESULTS: A total of 671 PCR analyses for *M. pneumoniae* were performed of which 102 tested positive (15%). Our study included 101 *M. pneumoniae*-positive children with a median age of six years (range: 57 days-16 years). The cases were distributed throughout the year, but with a peak from October to January. 43% were five years or younger, with 18% being 0-1 years old and almost 7% being less than one year old. Only 17% were 11-16 years old. 58% of the patients reported more than seven days of fever and/or cough prior to admission. In all, 65 of 101 *M. pneumoniae*-positive children were discharged within 24 hours of admission.

CONCLUSION: *M. pneumoniae* should be kept in mind as a cause not only of community-acquired pneumonia, but also of milder respiratory infections in children younger than five years. PCR from a nasal or throat swap is an easy, reliable and quick diagnostic test in infants and children.

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Mycoplasma pneumoniae is a common cause of community-acquired pneumonia and is transmitted by aerosol or close contact.

While pneumonia may be the most typical manifestation, children may more commonly have symptoms like cough and wheezing, often accompanied by symptoms of upper respiratory tract infection, and the symptoms mimic those seen in viral respiratory syndromes [1].

M. pneumoniae is endemic worldwide, but epidemics are common. In Denmark, regular epidemics of *M. pneumoniae* infection have been reported every four to seven years since 1949-50. With a few exceptions (1962-64 and 1971-73), the epidemics usually span only one winter [2].

In August 2010 an increase in the number of positive tests for *M. pneumoniae* was seen in Denmark, and several other European countries reported similar increases during the following months [3-8].

Historically, the highest prevalence of *M. pneumoniae* infection among children is found in school-aged children and young adults, among whom the prevalence rises with higher age. Recent studies, however, suggest that the infection may be under-diagnosed in children under the age of five years [3, 9].

Until the early 2000s, *M. pneumoniae* was diagnosed by serological testing in Denmark, but during the past decade, after documentation of its high sensitivity (88.2%) and specificity (100%), polymerase chain reaction (PCR) has gained a foothold [10]. In our department, PCR is now the standard method for diagnosis of *M. pneumoniae* respiratory infection.

The aim of this study was to describe the epidemiology and clinical course of respiratory tract infection (RTI) caused by *M. pneumoniae* in hospitalized children.

MATERIAL AND METHODS

In this retrospective descriptive study, we included all children hospitalized at the Department of Paediatrics at Hvidovre Hospital, Denmark, from 1 August 2010 to 30 May 2012 who tested positive for *M. pneumoniae* by PCR. All children were referred to our department from either the emergency department or a general practitioner. All infections were community-acquired. The decision to test for *M. pneumoniae* was based on the physician's clinical evaluation.

The typical specimen was a throat swab collected with a viscose swab, which was placed in a transport medium (UTM, Copan). Specimens were analysed for the presence of *M. pneumoniae* by a real-time PCR using a hydrolysis probe and targeting the gene encoding adhesin P1. All samples were also analysed for the presence of *Chlamydophila pneumoniae* and *Legionella* spp. by real-time-PCR.

ORIGINAL ARTICLE

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TABLE 1

Mycoplasma pneumoniae-positive patients.

	0-1 year	2-5 years	6-10 years	> 10 years	All
N (% of total)	18 (17.8)	25 (24.7)	41 (40.5)	17 (16.8)	101 (100)
Male, %	50	56	39	70	51
Chronic disease, n (%)	4 (22.2)	7 (28.0)	9 (22.0)	5 (29.4)	25 (24.8)
Symptoms > 7 days, n (%)	10 (55.6)	12 (48.0)	27 (65.9)	10 (58.8)	59 (58.4)
Fever > 38.0 °C, n (%)	8 (44.4)	9 (36.0)	17 (41.5)	8 (47.1)	42 (41.6)
Admitted > 24 h, n (%)	6 (33.3)	8 (32.0)	14 (34.2)	8 (47.1)	36 (35.6)
Oxygen supplement, n (%)	3 (16.7)	3 (12.0)	7 (17.0)	1 (5.9)	14 (13.9)
CPAP/PEP, n (%)	1 (5.6)	4 (16.0)	6 (14.6)	1 (5.9)	12 (11.9)
Tube feeding/parenteral fluid, n (%)	2 (11.1)	3 (12.0)	0 (0.0)	0 (0.0)	5 (5.0)
Complications, n (%)	1 (5.6)	5 (20.0)	7 (17.1)	1 (5.9)	14 (13.9)
Temp. at admission, °C, median (range)	38.0 (36.4-40.5)	37.8 (36.4-38.8)	37.9 (36.6-39.8)	38.2 (36.6-40.9)	37.9 (36.4-40.9)
CRP at admission, mg/l, median (range)	12 (1-65)	21 (0.3-77)	15 (0.3-48)	32 (5-82)	16 (0.3-83)
Total conc. of leukocytes at admission, $\times 10^9$/l, median (range)	10.4 (4.7-21.9)	10.5 (4.2-18.9)	9.15 (4.9-19.9)	8.1 (4.7-11.6)	9.6 (4.2-21.9)

CPAP/PEP = continuous positive airway pressure/positive expiratory pressure; CRP = C-reactive protein conc.

Demographic data included age, weight and sex. Admission-relevant data collected were duration of illness prior to admission, underlying chronic disease, C-reactive protein (CRP) and total white blood count at the time of admission. For patients hospitalized for more than 24 hours, the duration (days) of hospitalization, need for oxygen supply, other types of respiratory support, intravenous fluid, tube feeding, co-infections and complications were additionally recorded. Data were obtained from the medical charts. For all children, the type of medical treatment provided after confirmed microbiological diagnosis was noted.

Univariate statistical analysis of the data was performed using χ^2-test on categorical comparisons of two populations, and the Student t-test or the Mann Whitney U-test was used on continuous data. All tests were two-tailed and p values below 0.05 were considered significant. 95% confidence intervals were used.

Trial registration: not relevant.

RESULTS

From August 2010 through May 2012, a total of 671 PCR analyses for *M. pneumoniae* were performed and 102 tested positive (15%). In the subsequent data collection, one patient was excluded due to a missing medical chart.

Our study therefore included 101 *M. pneumoniae*-positive children (52% male) with a median age of six years.

The cases were distributed throughout the year, but with peaks from October to January, i.e. 84% of the cases were reported from late autumn to early winter.

Clinical characteristics stratified by age groups are shown in **Table 1**.

Patients

The median age of children with a positive PCR for *M. pneumoniae* was six years (57 days-16 years). 43% were five years or younger, with 18% being 0-1 years old and almost 7% being younger than one year. Only 17% were 11-16 years old.

The rate of positive tests compared to the total number of tests varied according to age with a low rate < 10% in infants under two years and up to more than 50% in adolescents (**Figure 1**).

Twenty-five children had previously been diagnosed with a chronic disease (Table 1). Of these, 8/25 (32%) had asthma or a history of recurrent chronic wheezing, and 2/25 (8%) had other chronic lung disease than the ones already mentioned, i.e. cystic fibrosis and bronchiectasias. 3/25 (12%) were born prematurely and 15/25 (60%) had other chronic diseases, e.g. reflex dystrophia, primary immunodeficiency or nephrotic syndrome. No children with congenital heart disease were found in our cohort.

The children with underlying chronic illness were not hospitalized longer than the otherwise healthy children (both groups a median of 0 days). Among the children needing hospitalization for > 24 hours, those with underlying chronic disease were hospitalized longer than the otherwise healthy children (a median of four days versus two days). However, this difference was not significant (p > 0.05, Mann Whitney U-test)

Clinical presentation and laboratory findings

In 59% of the cases, parents reported more than one week of fever and/or cough prior to admission. The remaining 41% reported symptoms for seven days or less. Fever was defined as a temperature of > 38.0°C. Temperature, C-reactive protein (CRP) and leukocyte-count

at admission were registered in most of the patients (92%, 85% and 82%, respectively). Of these, 42% were febrile at admission, 56% had increased CRP above normal and 15% had age-adjusted leukocytosis.

A total of 65 of 101 (64%) of *M. pneumoniae*-positive children were discharged within 24 hours of admission, 79 (89%) within 48 hours and only two children were admitted to the hospital for more than one week.

There was no difference in the duration of hospitalization between children < 5 year (median 0 days, range 0-6 days) compared with > 5 years (median 0 days, range 0-21 days, $p > 0.05$; Student's t-test).

Nearly 14% needed oxygen-supplementation to keep saturation levels above 93%. There was no difference in the rate between children younger or older than five years of age (13.9% versus 13.7%, $p > 0.05$; χ^2-test).

14% had complications; 13 children had X-ray verified atelectasis, one had empyema and one child had both. None of the children with empyema were tested for other aetiology. No neurological or other severe extra-pulmonary complications were seen in this population.

The rate of complications was the same for children younger and older than five years (13.9% versus 13.7%, $p > 0.05$; χ^2-test).

A total of 27 patients were tested for other respiratory aetiology, and co-infection was diagnosed in a total of 10%. Other pathogens found were respiratory syncytial virus (RSV), Influenza A and B, adenovirus, *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes* and *Bordetella pertussis.* Among the children with no confirmed co-infection, 81% were solely tested for atypical pneumonia.

The children with confirmed co-infection were significantly younger than the children without co-infection (3.7 years versus 6.6 years, $p = 0.02$; Student's t-test). While tests for other agents were performed in 48% of the *M. pneumoniae*-positive children aged 0-2 years, this was the case in only 13% of the children over two years of age.

70% of the children with confirmed co-infection were hospitalized for more than 24 hours and 40% needed oxygen supplement both of which are significantly more often than children without co-infection ($p = 0.03$, χ^2-test).

Treatment

A total of 99 children were treated with antibiotics. Three children were treated with intravenous antibiotics (cefuroxime), the remaining 97 with oral antibiotics. Two of the three children initially treated with intravenous cefuroxime were changed to oral macrolide after diagnosis.

The majority of the children (89%) were treated with macrolides: 37 with azithomycin, 45 with clarithromycin, five with erythromycin, one with roxithromycin and two with unspecified macrolides.

Six patients were treated only with beta-lactams with reported good effect. One child was treated with flourquinolone.

Only one patient received no medical treatment due to full spontaneous recovery when the *M. pneumoniae*-positive result was available.

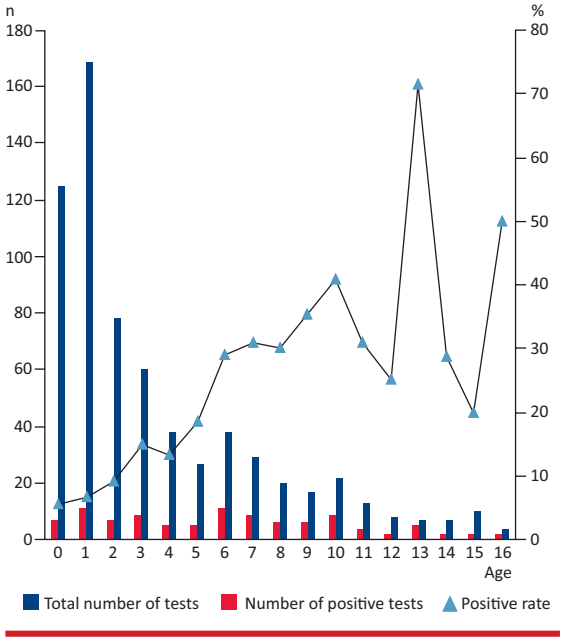
DISCUSSION

This study was performed to describe the characteristics of hospitalized children positive for *M. pneumoniae* and clinical signs of RTI. During the 22 month data collection period, 15% were found to be infected with *M. pneumoniae.*

The incidence of hospitalized adolescents found in the present study as well as in other reports [1, 9] may be explained by the fact that immunity appears to increase progressively with age [7, 11]. Yet bias due to this study being performed at a hospital after referral from a primary physician cannot be ignored. Adolescents with *M. pneumoniae* are well-described in the literature and present with classical symptoms. Thus, the majority of these adolescents may already have been diagnosed and treated by the primary physician. Another limitation in this study is the lack of information on who of the children were examined for *M. pneumoniae* infection once admitted to the hospital. As PCR for *M. pneumoniae* is

FIGURE 1

Positive rates by age.



Mycoplasma pneumoniae infection may mimic viral respiratory syndromes in children and infants.

not a routine test at admission due to RTI at our department, the tests has been performed following an individual assessment not evident by retrospective chart review.

We found a high rate of infected infants. Thus, 18% of our cohort were one year or younger, the youngest being only 57 days old. 43% of our cohort was five years old or below. There was no apparent difference in morbidity between the two groups.

Similar rates were found in an Australian study from 2005 among children presenting to a tertiary children's hospital with *M. pneumoniae* infection, where 39% were less than five years old [1]. Notably, no infants less than six months of age were diagnosed in the Australian cohort. Also, an Italian study from 2008 confirmed our results by finding 38.2% preschool-aged children (< 5 years). Of these, 21.6% were less than 24 months old [9].

During the current epidemic in Scotland, 24.9% were found to be 0-4 years old [3]. Like in our study, the majority of the children in both the Scottish and the Italian study were diagnosed from respiratory PCR-positive specimens as opposed to serology which was used in the Australian study.

Conversely, Almasri et al found merely 6.8% under three years old [12] and the majority of the affected children were school-aged. Likewise, surveillance data from England and Wales in 2011-2012 found that detectable *M. pneumoniae* infection was absent in those < 4 years [8]. These findings are in line with the historical understanding [8, 11].

We hypothesise that infants may previously have been under-diagnosed due to differences in diagnostic methods. Thus, studies suggest that PCR can detect even mild cases of infection in which a detectable immune response is lacking [13, 14]. Other studies indicate that immaturity of the immune system may precipitate negative serology, but still show positive PCR for *M. pneumoniae,* just as studies have shown a lack of antibody response to *M. pneumoniae* particularly for all immuno-compromised infants and infants below 12 months of age [12, 13]. Other studies based on serology support this hypothesis by not finding any or only very few seropositive children below two years of age [1, 12, 15].

Gadsby et al found significantly fewer *M. pneumoniae* reports from serology than from respiratory specimens in children aged 0-4 years, and they therefore concluded that respiratory specimens for PCR are more easily obtained than blood specimens in infants. *M. pneumoniae* infections in this age-group may therefore be under-diagnosed in hospitals where only serological testing is available [3].

Infants might therefore at present be under-diagnosed due to "doctors' bias" as the conventional assumption that *M. pneumoniae* is rare in pre-school aged children and infants may well prevent many physicians form considering *M. pneumoniae* as a differential diagnosis in this age group.

A rapid increase of macrolide-resistant *M. pneumoniae* has been reported from Asia in recent years, but macrolide resistance is also seen in Europe and in the United States [16]. The latest data from the 2010-11 epidemics from the Danish National Institute for Health Data and Disease Control (SSI) found 1-3% of macrolide resistance, whereas no resistance was found in England and Wales [8, 17]. In our study we did not examine the samples for macrolide resistance, but one case was treated with flourquinolone due to suspected resistance and previous unsuccessful treatment with macrolide.

The rate of chronic illness, the duration of hospitalization, oxygen requirements, the rate of complications and paraclinical findings were consistent with findings in the international literature. No clinical or laboratory findings other than positive serology or PCR have been shown to significantly indicate *M. pneumoniae* [12, 14, 18]. The relative placidity of the disease, however, suggests that *M. pneumoniae* infection is less severe than other pulmonary bacterial infections, but more similar to viral infection in children [18, 19].

This mild course was not only seen in older children, but also among the youngest infants as there was no significant difference in the need for oxygen-supplement, days of hospitalisation or complications. We did find a

significant difference in age and need for oxygen and hospitalization of co-infected versus not co-infected children. However, this result is probably more an illustration of the less characteristic course in young children rather than an indication of an increased rate of co-infections as the result may be biased by more extensive investigations in young children. Likewise, more extensive testing may be performed in children who present as clinically more ill.

In conclusion, PCR from a nasal or throat swap is an easy, reliable and quick diagnostic test in infants and children suspected of *M. pneumoniae* infection. Awaiting PCR diagnosis before initiating antibiotic therapy may be regarded as safe considering the relatively benign nature of the infection.

Importantly, *M. pneumoniae* should be considered as a cause not only of community-acquired pneumonia, but also of milder respiratory infections in children less than five years old.

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