Epidemiological and Clinical Feature of Respiratory Tract Infections Caused by Mycoplasma Pneumoniae in a Pediatric Emergency Department

Raz Oron MD[a], Meirav Mor MD[a], Zmira Samra PhD[b,c], Lisa Amir MD FAAP[a], Marc Mimouni MD[a] and Yehezkel Waisman MD[a]

[a] *Department of Emergency Medicine, Schneider Children's Medical Center of Israel, Petah Tiqwa, ISRAEL*
[b] *Microbiology Laboratory, Rabin Medical Center, Beilinson Campus, Petah Tiqwa, ISRAEL*
[c] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, ISRAEL

Abstract

Objective: To characterize the epidemiological and clinical features of respiratory tract infections caused by Mycoplasma pneumoniae in children visiting the emergency department. *Study Design:* Prospective clinical study.
Study Population and Setting: Children 1 month to 18 years of age who presented to the emergency department of an urban pediatric tertiary facility with symptoms and signs of a respiratory tract infection between September 2000 and February 2001.
Patients and Methods: 100 children with at least one of the following: 1) cough and/ or coryza; 2) stridor or wheezing with fever, or 3) physical findings consistent with pneumonia. Patients pretreated with macrolides were excluded. Laboratory work-up included at least a complete blood count. Serologic study, nasopharygeal culture, and chest x-ray were performed in all cases. Clinical, radiological, laboratory, and epidemiological parameters were collected from the files and compared between patients with Mycoplasma and non-Mycoplasma pneumonia.
Results: Twenty patients (20%) had a positive serologic finding for M pneumoniae, including 16 (80%) with a clinical diagnosis of pneumonia, who accounted for 25% of the total patients with pneumonia. Twelve were <5 years old and 6 were >3 years old. Patients with Mycoplasma pneumonia had a significantly longer duration of fever prior to admission (3.6 vs 2.2 days, $p=0.025$), higher rate of auscultatory findings consistent with pneumonia (63% vs 15%, $p<0.002$), and higher rate of atelectasis (38% vs 2%, $p<0.001$) than patients with non-Mycoplasma pneumonia. There were no significant differences between the groups in any of the other parameters. Only 4 children (25%) with *Mycoplasma* pneumonia recieved specific antibiotic (macrolide) therapy at discharge.
Conclusions: The prevalence of Mycoplasma respiratory tract infection in young children (ages 3-5) appears to be higher than originally thought. We suggest that macrolide therapy be considered in these age groups, especially in the presence of positive auscultatory findings or atelectasis.

MeSH Words: Emergency department; Mycoplasma Pneumoniae; Community-Acquired Pneumonia; Upper Respiratory Tract Infection; Emergency Medicine; Children.

Introduction

In the 1960s and 1970s, *Mycoplasma pneumoniae* infections occurred in 3-to-4-year epidemic cycles with seasonal periodicity. Since then, however, large population studies have reported a shift to an endemic pattern [1-4]. *M pneumoniae* is well recognized as the most common etiological agent of community-acquired pneumonia (CAP) in hospitalized and non-hospitalized children aged 5-15 years. Its prevalence in younger children, once considered

rare, appears to be increasing as well. In community-based studies conducted over the last 15 years, *M pneumoniae* accounted for 1.5-25% of all cases of CAP in the under-5-year age group, and 3-22% in the under-3-year age group [5-11]. Traditionally, treatment of CAP consists of amoxicillin and amoxicillin/clavulanate, although macrolides have recently shown equal efficacy [10-13]. Considering the growing prevalence of *M pneumoniae* infection in the younger age groups, macrolides may be justified as the first-choice treatment for CAP and its management in the emergency department (ED) in infants and children.

The aim of this study was to characterize the epidemiological and clinical features of respiratory tract infections caused by *M pneumoniae* in children visiting the ED.

Patients and methods

The study group included 100 consecutive children that presented to the ED of an urban pediatric tertiary care facility during the primary investigator ED shifts, between September 2000 and February 2001. The patients were children aged 1 month to 18 years, with symptoms and signs of respiratory tract infection. Children with at least one of the following were included: 1) cough or coryza; 2) stridor or wheezing with fever; 3) physical findings consistent with pneumonia. Patients pre-treated with macrolides or hospitalized in the past month were excluded. Laboratory work-up included at least a complete blood count; additional blood tests were performed at the discretion of the treating physician in the ED. A serologic study, nasopharyngeal swab for *Mycoplasma* culture, and a chest radiograph were performed in all cases. The diagnosis of *M pneumoniae* infection was made on the basis of a single serology test. Pneumonia was diagnosed by findings of fever and parenchymal infiltrates on the chest radiograph [12,14]. Antibiotics were administered at the discretion of the treating physician. The serology test results were not available to the treating physician upon ED discharge.

The patient files were reviewed for clinical, radiological, laboratory, and epidemiological parameters, and patients with *Mycoplasma* pneumonia (MPP) or non-*Mycoplasma* pneumonia (NMPP) were compared. Data were statistically analyzed using BMDP statistical software [15]. Pearson's R2 test or Fisher's exact test, the long-linear model, and one- and two-way ANOVA were performed, as necessary.

The study was approved by the institution's ethics committee.

Results

The distribution of patients by specific diagnoses and serologic evidence of *Mycoplasma* infection is shown in Table 1. Serology was positive for *M pneumoniae* in 20 patients (20%) and borderline in 4 patients (4%). Nasopharyngeal cultures were positive for *M pneumoniae* in only 4 out of these 20 patients. Only the patients with clearly positive findings were included in the statistical analysis.

Sixteen of the 20 seropositive patients (80%) had pneumonia and 4 (20 %) had an upper respiratory tract infection. Ages ranged from 9 months to 17 years (median 51 months); 12 patients (60%) were <5 years old, and 6 (30%) were <3 years old. There was no significant difference in the monthly occurrence of *M pneumoniae* infection (data not shown).

Pneumonia was diagnosed in 64 children, of whom 13 (20%) were <5 years old and 8 (13%) were <3 years old. The 16 patients with MPP accounted for 25% of all children with pneumonia; the other 48 had NMPP. Table 2 shows the distribution of seropositivity among patients with pneumonia by age.

The main epidemiological, clinical, and radiological characteristics of the patients with *Mycoplasma* and *non-Mycoplasma* CAP are summarized in Table 3. Significant differences between the two groups were noted only for duration of fever before admission ($p=0.025$), auscultatory findings consistent with pneumonia ($p<0.002$), and presence of atelectasis ($p<0.001$).

The antibiotic therapy prescribed to the children with pneumonia at discharge from the ED is presented in Table 4. Only 4 children with MPP (25%) received macrolide therapy.

Table 1. Distribution of diagnoses and percentage of *M pneumoniae* seropositivity in 100 children with respiratory tract infection

Diagnosis	No. (%) of patients	No. (%)* of *MP* seropositive patients
Pneumonia	64 (64%)	**16 (25%)**
URTI	30 (30%)	**4 (13.3%)**
Laryngitis	4 (4%)	**0**
Laryngotracheobronchitis	1 (1%)	**0**
Bronchiolitis	1 (1%)	**0**
Total	100 (100%)	20 (20%)

* Percentage of *M pneumoniae* seropositive patients among all patients with the specific diagnosis URTI-upper respiratory tract infection

Table 2. Percentage of *M pneumoniae* seropositive patients among all patients with pneumonia by age group

Age (Yr)	*MP* seropositive (%)*
All patients (median age 43 months)	25% (16/64)
<3 yrs	13% (6/45) (+ 7% - Borderline)
0-6 month	0% (0/6)
7-12 month	17% (3/17)
13-36 month	14% (3/22)
3-5 yrs	46% (6/13)
>5 yrs	**67% (4/6)**

*Numbers in parentheses indicate number of seropositive patients out of total number of patients with pneumonia in that age group.

Table 3. Epidemiological, clinical, and radiological characteristics of MPP and NMPP pneumonia patients

Parameter*	MPP n = 16	NMPP N = 48	P
Fever at ED admission (^{0}C)	38.7 ± 0.7	39.1 ± 0.8	**NS**
Duration of fever before admission (days)	3.6 ± 2.8	2.3 ± 1.6	**P = 0.025**
Duration of cough before admission (days)	5.4 ± 4.7	4.3 ± 2.9	**NS**
Duration of rhinorrhea before admission (days)	1.9 ± 3.8	1.5 ± 2.4	**NS**
Previous antibiotic therapy	31%	19%	**NS**
Mean duration of previous antibiotic therapy (days)	1.4 ± 2.4	0.5 ± 1.3	**NS**
Close contact with a coughing relative	50%	38%	**NS**
History of asthma	31%	19%	**NS**
Tachypnea/Dyspnea	19%	25%	**NS**
Hypoxemia (saturation < 95%)	6%	8%	**NS**
Wheezing at admission	60%	56%	**NS**
Auscultatory findings consistent with pneumonia	63%	31%	**P <0.002**
Mean WBC (10^3/ml^3)	15.4 ± 9.2	15.2 ± 8.1	**NS**
WBC >15000/ml^3	50%	35%	**NS**
PMN >70%	25%	21%	**NS**
PLT >450000/ml^3	19%	17%	**NS**
Bilateral CXR infiltrates	50%	64%	**NS**
Multiple CXR infiltrates	38%	48%	**NS**
Alveolar CXR infiltrates	31%	35%	**NS**
Interstitial CXR infiltrates	25%	17%	**NS**
Mixed CXR infiltrates	44%	48%	**NS**
Atelectasis	**38%**	**2%**	**P <0.001**

*Figures represent mean±SD or n(%), as indicated.
ED-emergency department, WBC-white blood count, PMN-polymorphonuclears, PLT-platelets, CXR-chest x-ray

Table 4. Antibiotic therapy prescribed to children with pneumonia (% of patients)

Type of pneumonia	No antibiotic therapy	Macrolide & azalide* antibiotic	Other antibiotic**
NMPP (n=48)	12 (25%)	17 (35%)	19 (40%)
MPP (n=16)	**3 (19%)**	**4 (25%)**	**10 (56%)**

***** Erythromycin, azithromycin, clarithromycin
**Beta lactams: amoxicillin, amoxicillin-clavulanate, cefuroxime, ceftriaxone
NMPP-non-*Mycoplasma pneumoniae* pneumonia; MPP- *Mycoplasma pneumoniae* pneumonia

Discussion

This study examined the clinical, radiological, and epidemiological characteristics of children with MPP and NMPP. We found that of the children who were seropositive for *M pneumoniae*, 20% were <5 years of age and 13% were <3 years of age; another 7% had borderline findings. Our findings are consistent with the 14-25% rate of *Mycoplasma* CAP reported in the literature [7-10,12]. Furthermore, of the total children with pneumonia aged 3-5 years in our sample, 46% were seropositive for *M pneumoniae* (Table 2) – higher than previously reported. The increasing rate of MPP in young children may be explained by the changing epidemiology of *Mycoplasma* infection to a relatively constant endemic pattern [1-4], along with the increase in attendance at day care centers at young ages [22], which causes frequent infectious episodes. Accordingly, the transmission rate in families of index cases with *Mycoplamsa* upper respiratory tract infection is as high as 80%, mainly in children [23,24]. An asymptomatic carrier state can persist for several months after *Mycoplasma* infection, especially in children under 5 years of age [25].

The duration of fever before admission was significantly longer in children with MPP than in children with NMPP (3.6 vs. 2.3 days, respectively, p=0.025, Table 3). A similar finding was reported by Fischer et al. [26] in a prospective cohort study of 253 ambulatory children with CAP. The authors created two systems to predict the risk of MPP: a simple scoring system and a fast decision tree based on the duration of fever and patient age. In the decision tree, fever for more than two days implied a moderate to high risk for MPP, which is consistent with our findings.

The study also yielded another important clinical finding. Although most authors reported no differences in the clinical presentation of MPP and NMPP [3,8,10], in our series, auscultatory findings and atelectasis on x-ray film were consistently associated with MPP as opposed to NMPP. We were able to identify only one other study by John et al. [27] that reported a similarly high atelectasis rate in MPP. Nevertheless, it should be borne in mind that MPP cannot be differentiated from "typical" bacterial or viral pneumonia by the radiological presentation alone [11,27,28].

Interestingly, despite the high infectivity of *MP* respiratory infections [23-25], close contact with a coughing relative was not significantly more common in the MPP than the NMPP subgroup (Table 3). This finding agrees with the study of Principi et al [8]. History of asthma and exacerbation of asthma were also not significantly more prevalent in the MPP group (Table 3). The relationship between *M pneumonia* respiratory tract infection and asthma remains controversial [11,14,17,29].

All laboratory parameters were similar in the MPP and NMPP groups (Table 3). Previous studies, too, have shown that that total white blood cell count, percentage or total number of neutrophils, erythrocyte sedimentation rate, C-reactive protein level, and platelet count are not useful for differentiating among pneumonia due to *Mycolasma*, other bacterial agents or viral agents [8,10,11,18,21,26,30,31].

The identification of the etiological agent of CAP in children is a challenge to clinicians because of the nonspecific nature of the clinical, laboratory, and radiology findings, the difficulty in obtaining culture samples, the long time before results of cultures and serologic assays

become available, the high cost of the more advanced assays [19], and the often mixed cause of respiratory tract infections [11]. As a result, the treatment of childhood CAP is almost always empirical. The choice of antibiotic therapy must therefore be based on a combination of several factors, including patient age, the epidemiologic pattern of various pathogens in the specific geographic area, the clinical presentation, and the local resistance patterns of predominant bacterial pathogens [14, 18-20, 32]. There have been only a few attempts to introduce practical guidelines for the empirical treatment of childhood CAP in the developed world, with no agreement [14,20,32].

Age is the best single predictor of the etiology of childhood CAP and a key point in the therapeutic decision [20]. Macrolides are probably the treatment of choice in CAP for outpatients aged 5 years or more [14, 20 , 32]. Only one practical guideline suggested macrolides as an equal alternative to amoxicillin in children under 5 years of age [20]. Large prospective randomized trials demonstrated an equal efficacy (clinical and radiological), and significantly fewer side effects, of azithromycin and clarithromycin compared to amoxicillin and amoxicillin\clavulanate in the treatment of CAP in ambulatory nontoxic children age 6 months and older [10-13].

The macrolide antibiotics have good activity against bacterial and atypical pathogens in upper and lower respiratory tract infections in children [33]. However, the recent rise in macrolide use worldwide has been followed by a sharp increase in macrolide-resistant *S pneumoniae* isolates, particularly in children under 5 years of age [34]. A similar rise was demonstrated for group A *Streptococcus* [35]. Seppala et al. [36] demonstrated that a nationwide reduction in the use of macrolide antibiotics for outpatient therapy in Finland was correlated with a significant decline in the frequency of erythromycin resistance among group A *Streptococcus* isolates. The physician should take into account all the above mentioned factors, before prescribing antibiotic therapy for CAP.

The limitations of our study are a relatively small number of participants and the diagnosis of *M pneumoniae* infection on the basis of a single positive serology test. We chose this method instead of paired sera or polymerase chain reaction [3,5,9,11,12,19,24,27,29] because the study was conducted in the emergency department setting. None of the available methods is considered 100% diagnostic.

We also obtained nasopharyngeal cultures for *Mycoplasma*, but findings were positive in only 4 cases (data not shown). This may be due to the difficulty of culturing of *Mycoplasma*. It is also possible that some of the patients had had a recent *M pneumoniae* infection which may have predisposed them to pneumonia, such that *M pneumoniae* was not the causative agent of their CAP.

On the other hand, serology tests for *Mycoplasma* turn positive within several days of disease, and most of our patients were evaluated less than 7 days from disease onset. Thus, the prevalence of *Mycoplasma* infection may have been even higher than shown here. It is certainly possible that the borderline test results, which were excluded from the statistical analysis, would have been positive had they been performed several days later.

The relatively high prevalence of MPP in young children (<3 years old) and the clinical and radiographic findings consistent with *M pneumoniae* infection have important clinical implications. We recommend that macrolides be considered for the treatment of CAP in selected nontoxic children aged 3 years or older, especially in the presence of aucultatory findings consistent with pneumonia or atelectasis. The ED is typically seen as a setting for acute and frequently intensive management of patients. However, the ED is increasingly used as a place in which, less by design than because of prevailing resource issues, patients are allowed to die [15]. Medical management of the dying patient is traditionally the role of the palliative care service, which may take place on a conventional medical or surgical inpatient unit, or in a designated Palliative Care Unit. There is a growing need for Emergency Physicians to be

comfortable in managing those patients for whom there is no prospect of curative treatment. At present, there is a paucity of literature regarding terminal care in the ED [16].

References

1. Ito I, Ishida T, Osawa M. Culturally verified Mycoplasma pneumonia in Japan: a long term observation from 1979-99. Epidemiol Infect, 2001; 127:365-7.

2. Foy HM. Infections caused by *Mycoplasma pneumonia* and possible carrier state in different populations of patients. Clin Infect Dis, 1993; 17:537-46.

3. Lind K, Bentzon MW, Jensen JS. A seroepidemiological study of *Mycoplasma pneumonia* infections in Denmark over the 50-year period 1946-1995. Eur J Epidemiol, 1997; 13:581-6.

4. Rastawicki W, Kaluzewski S, Jagielski M. Occurrence of serologically verified *Mycoplasma pneumonia* infections in Poland in 1970-1995, 1998; 14:37-40.

5. Heiskanen-Kosma T, Korppi M, Jokinen C. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. Pediatr Infect Dis J, 1998; 17:986-91.

6. Claesson BA, Trollfors B, Brolin I. Etiology of community-acquired pneumonia in children based on antibody responses to bacterial and viral antigens. Pediatr Infect Dis J, 1989; 8:856-62.

7. Nagayama Y, Sakurai N, Yamamoto K. Isolation of *Mycoplasma pneumonia* from children with lower respiratory tract infections. J infect Dis, 1988; 157:911-7.

8. Principi N, Esposito S, Blasi F. Role of *Mycoplasma pneumonia* and *Chlamydia pneumonia* in children with community-acquired lower respiratory tract infections. Clin Infect Dis, 2001; 32:1281-9.

9. Baer G, Engelcke G, Abele-Horn M. Role of *Chlamydia pneumonia and Mycoplasma pneumonia* as causative agents of community-acquired pneumonia in hospitalized children and adolescents. Eur J Clin Microbiol Infect Dis, 2003; 22:742-5.

10. Block S, Hedrick J, Hammerschlag M. *Mycoplasma pneumonia* and *Chlamydia*

pneumonia in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. Pediatr Infect Dis J, 1995; 14:471-7.

11. Wubbel L, Muniz L, Ahmed A. Etiology and treatment of community-acquired pneumonia in ambulatory children. Pediatr Infect Dis J, 1999; 18:98-104.

12. Harris JA, Kolokathis A, Campbell M. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatr Infect Dis J 1998;17:865-71.

13. Kogan R, Maritinez MA, Rubilar L. Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of community-acquired pneumonia in children. Pediatr Pulmonol, 2003; 35:91-8.

14. McIntosh K. Community-acquired pneumonia in children. N Engl J Med, 2002; 346:429-37.

15. BMDP Statistical Software, 1993. Chief Editor: W.J. Dixon. University of California Press, Los Angeles, CA.

16. Murphy TF, Henderson FW, Clyde WA Jr. Pneumonia: an eleven-year study in a pediatric practice. Am J Epidemiol, 1981; 113:12-21.

17. Jokinen C, HeiskanenL, Juvonen H. Incidence of community-acquired pneumonia in

the population of four municipalities in eastern Finland. Am J Epidemiol, 1993; 137:977-88.

18. Isaacs D. Problems in determining the etiology of community-acquired childhood pneumonia. Pediatr Infect Dis J, 1989; 8:143-8.

19. McCracken GH Jr. Diagnosis and management of pneumonia in children. Pediatr Infect Dis J, 2000; 19:924-8.

20. Jadavji T, Law B, Lebel MH. A practical guide for the diagnosis and treatment of pediatric pneumonia. CMAJ, 1997; 156:S703-11.

21. Nohynek H, Valkeila E, Leinonen M. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing

etiologic diagnosis of acute lower respiratory infections in children. Pediatr Infect Dis J, 1995; 14:484-90.

22. Lind K, Bentzon MW. Changes in the epidemiological pattern of *Mycoplasm pneumonia* infections in Denmark. A 30 years survey. Epidemiol Infect, 1988; 101:377-86.

23. Hanukoglu A, Hebroni S, Fried D. Pulmonary involvement in *Mycoplasma pneumonia* infection in families. Infection, 1986; 14:1-6.

24. Dorigo-Zetsma JW, Wilbrink B, van der Nat H. Results of molecular detection of *Mycoplasma pneumonia* among patients with acute respiratory infection and in their household contacts reveals children as human reservoir. J Infect Dis, 2001; 183:675-8.

25. Foy HM. Infection caused by *Mycoplasma pneumonia* and possible carrier state in different populations of patients. Clin Infect Dis, 1993; 17(supp):37-46.

26. Fischer JE, Steiner F, Zucol F. Use of simple Heuristics to target macrolide prescription in children with community-acquired pneumonia. Arch Pediatr Adolesc Med, 2002; 156:1005-8.

27. John SD, Ramanathan J, Swischuk LE. Spectrum of clinical and radiographic findings in pediatric *Mycoplasma pneumonia* pneumonia. Radiographics, 2001; 21:121-31.

28. Guckel C, Benz-Bohm G, Widemann B. Mycoplasmal pneumonias in childhood: roentgen features, differential diagnosis and review of literature. Pediatr Radiol 1989; 19:499-503.

29. Waites KB. New concepts of *Mycoplasma pneumonia* infections in children. Pediatr Pulmonol, 2003;36:267-78.

30. Drummond P, Clark J, Wheeler J. Community acquired pneumonia – a prospective UK study. Arch Dis Child, 2000; 83:408-12.

31. Clements H, Stephenson T, Gabriel V. Rationalised prescription for community acquired pneumonia: a closed loop audit. Arch Dis Child, 2000; 83:320-4.

32. Dagan R. Antibiotic treatment of pediatric community-acquired lower respiratory tract infections: challenges and possible solutions. Respiration, 1993; 60(supp):38-44.

33. McCracken GH Jr. Microbiologic activity of the newer macrolide antibiotics. Pediatr Infect Dis J, 1997; 16:432-7.

34. Hyde TB, Gay K, Stephens DS. Macrolide resistance among invasive streptococcus pneumonia isolates. JAMA, 2001; 286:1857-62.

35. Martin JM, Green M, Barbadora KA. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. N Engl J Med, 2002; 346:1200-6.

36. Seppala H,Klukka T, Vuopio-Varkila J. The effect of changes in the consumption of macrolides antibiotics on erythromycin resistance in group A streptococci in Finland. N Engl J Med, 1997; 337:441-6.

Competing Interests: None declared.

Funding: None

This manuscript has been peer reviewed

Correspondence:

Y. Waisman, M.D.
Unit of Emergency Medicine
Schneider Children's Medical Center of Israel
14 Kaplan Street
Petah Tiqwa 49202, Israel

Tel: +972-3-9253661
Mobile phone: +972-54-7541540
Fax: +972-3-9223011
E-mail: waisy@clalit.org.il