MYCOPLASMA PNEUMONIAE INFECTION IN MALAYSIAN CHILDREN ADMITTED WITH COMMUNITY ACQUIRED PNEUMONIA

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Abstract. *Mycoplasma pneumoniae* is increasingly recognized as an important cause of community acquired pneumonia (CAP) in children. We determined the importance of *M. pneumoniae* as a causative agent in 170 children aged 1 month to 15 years who were hospitalized with CAP over a 6-month period. The diagnosis of *M. pneumoniae* infection was based on serological evidence obtained by a particle agglutination test (SERODIA-MYCO II). A positive serological diagnosis was made if the acute phase serum titer was more than 1:160 or paired samples taken 2-4 weeks apart showed a four-fold or greater rise in the serum titer. *M. pneumoniae* was identified as the causative agent in 40 (23.5%) children. Children with *M. pneumoniae* infection were more likely to be older than 3 years (OR 4.0 95%CI 1.8-9.1, p<0.001), Chinese (OR 4.3 95%CI 2.0-8.9, p<0.001), have a duration of illness longer than 7 days prior to admission (OR 6.0 95%CI 2.7-13.5, p<0.001) and have perihilar interstitial changes on chest X-ray (OR 4.6 95%CI 2.2-9.9, p<0.001). A significant number of hospital admissions for CAP in Malaysian children can be attributed to *M. pneumoniae*. It is important to identify these children so as to administer the most appropriate antibiotic treatment.

INTRODUCTION

Community acquired pneumonia (CAP) is a common cause of childhood illness requiring hospital admission. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the two most important organisms responsible for bacterial childhood CAP especially in developing nations (Berman, 1991; Shann, 1995). *M. pneumoniae* is increasingly recognized as an important cause of CAP in older children, especially in the more developed nations (Kayser, 1992; McCracken, 2000). Malaysia is rather in a unique position as its infrastructure and socio-economic character are in the process of evolving into a modern, developed country, most evident in the large cities like Kuala Lumpur. However, information on the importance of *M. pneumoniae* as a cause of childhood CAP in this region especially Malaysia is rather limited.

We therefore set out to determine the importance of *M. pneumoniae* infection in children hospitalized with a diagnosis of CAP. Clinical parameters associated with *M. pneumoniae* infection were also evaluated.

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MATERIALS AND METHODS

Patient population

The University Malaya Medical Center (UMMC) is situated in Kuala Lumpur, the capital of Malaysia and provides primary health care services to a predominantly urbanized society. All children aged 1 month to 15 years who were admitted with a diagnosis of community acquired pneumonia to the Department of Pediatrics, UMMC over a 6-month period were prospectively enrolled into the study. All these children presented with a fever of more than 37.5ºC with respiratory symptoms and had respiratory signs or chest

radiograph changes compatible with a diagnosis of pneumonia. Investigations performed for all subjects included a full blood count, serum electrolytes, nasopharyngeal secretion for respiratory viruses immunofluorescence test, blood culture and chest X-ray. There was no epidemiological evidence of an outbreak of respiratory infection in the city during the study period.

Diagnosis of *M. pneumoniae* infection

The diagnosis of *M. pneumoniae* infection was based on serological evidence obtained with a passive particle agglutination test (SERODIA-MYCO II, Fujirebio Inc, Tokyo, Japan). Acute and convalescent phase blood samples were collected and tested for *M. pneumoniae*-specific antibodies according to the manufacturer's instructions. A single antibody titer of more than 1:160 or a ≥ 4 fold rise in antibody titer in blood samples taken 2-4 weeks apart was considered as positive for *M. pneumoniae* infection. The diagnostic cut-off titer of 1:160 was chosen based on a previous study which showed that the manufacturer's recommended cut-off titer of 1:40 was too low as it was found in 45% of healthy blood donors. A titer of 1:160 was found in less than 10% of the healthy population studied (Tay and Cheong, 1995).

Statistical analysis

Results were analyzed using the statistical programme SPSSWIN version 7.5 (SPSS Inc, Chicago IL, USA) for Windows operating system 1998. The Student's *t*-test was used for quantitative data and the Fishers exact and chi-square test was used to compare proportions where appropriate. The likelihood of various parameters associated with *M. pneumoniae* infection was described with odd ratios and 95% confidence intervals using univariate analysis. A p-value of less than 0.05 was considered significant.

RESULTS

A total of 170 children admitted during the study period were analysed. Forty (23.5%) children had serological evidence of *M. pneumoniae* infection (Table 1). Children with positive *M. pneumoniae* serology were more likely to be older (mean age 6.3 ± 3.5 *vs* 3.5 ± 2.1 years, $p < 0.001$) and the prevalence of antibodies increased with age (Fig 1).

M. pneumoniae was more likely to be the causative agent for CAP in children who were

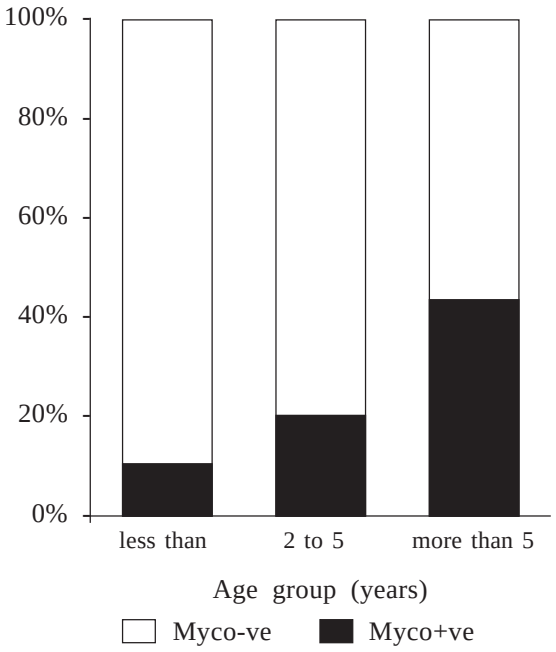

Fig 1–Prevalence of *M. pneumoniae* seropositvity and age group in 170 children admitted with community acquired pneumonia.

Table 1
Antibody titers of 40 children with *M. pneumoniae* infection.

Antibody titer	Number (%)
1 : 160	2 (5)
1 : 320	8 (20)
1 : 640	7 (18)
1 : 1,280	3 (8)
1 : 2,560	3 (8)
1 : 5,120	4 (10)
4 fold rise in acute and convalescent samples	13 (31)

Table 2
Clinical factors associated with *M. pneumoniae* infection in 170 children admitted with community acquired pneumonia.

Clinical parameters	*M. pneumoniae* serology positive (n = 40)	*M. pneumoniae* serology negative (n = 130)	OR (95%CI)	p-value
Age > 3 years	31 (82%)	61 (46%)	4.0 (1.8-9.1)	<0.001
Sex				
Boys	28 (70%)	84 (65%)	1.3 (0.6-2.7)	0.708
Girls	12 (30%)	46 (35%)	0.8 (0.4-1.7)	0.846
Ethnicity				
Malay	12 (30%)	75 (58%)	0.3 (0.1-0.7)	0.003
Chinese	22 (55%)	29 (22%)	4.3 (2.0-8.9)	<0.001
Indian	6 (15%)	26 (20%)	0.7 (0.3-1.8)	0.814
Duration>7 days	19 (48%)	17 (13%)	6.0 (2.7-13.5)	<0.001
Wheeze	11 (28%)	54 (42%)	0.6 (0.8-1.2)	0.171
Perihilar infiltrates (CXR)	21 (53%)	28 (22%)	4.6 (2.2-9.9)	<0.001

more than 3 years and who were Chinese. CAP with a duration of illness of more than 7 days and chest X-ray showing peri-hilar infiltrates were also more likely to be seen in *M. pneumoniae* infection (Table 2). There was no difference in the mean hemoglobin (121 ± 13 *vs* 115 ± 18 g/l, p = 0.17), total white count (13.5 ± 8.1 *vs* 22.9 ± 17.3 x 10^{9}/l, p = 0.31) and serum sodium concentration (139 ± 6 *vs* 137 ± 15 mmol/l, p = 0.45) between children with *M. pneumoniae* infection and those without. There was also no difference in the positive detection rate of respiratory viruses between these two groups (2.6% *vs* 3.0%, p = 0.81).

Extra-pulmonary complications were encountered in 3 (8%) children with *M. pneumoniae* infection. Two children had elevated liver enzymes that normalized after 1 week. A 6-year-old girl with *M. pneumoniae* infection developed hemolytic anemia, shock, liver failure and cardiac failure and succumbed to multi-organ failure on day 15 of illness.

DISCUSSION

There is no doubt that lower respiratory tract infection, especially pneumonia, continues to be a common and important cause of morbidity in children worldwide. Nonetheless, marked differences in the epidemiology, etiology and severity or burden of illness exist between nations and regions separated by their individual socioeconomic, genetic and climatic parameters. The diagnosis and management of children with CAP are further complicated by the difficulty in identifying the definite causative organism responsible for the illness (Isaacs, 1989); recent developments have however introduced increasing dependence on serological methods for pathogen identification. Serological diagnosis is particularly important for *M. pneumoniae* as the development of an isolation and culture technique that is simple, cost-effective and successful remains elusive. The SERODIA-MYCO II test is widely used because it is available commercially and simple to use. More importantly, this test and its appropriate serological cut-off titer has been validated in and epidemiological survey of healthy individuals in Malaysia (Tay and Cheong, 1995). Its sensitivity and specificity of 90% and 94% are additional features that make its application in clinical practice useful (Kennedy *et al*, 1990).

Streptococcus pneumoniae and *Haemo-*

philus influenzae are regarded the more common etiological agents of CAP but *M. pneumoniae* has recently been consistently found to be as important, especially in older children. Serological evidence suggests that between 20 - 35% of CAP in children may be attributed to *M. pneumoniae* (Foy *et al*, 1979; Heiskanen-Kosma *et al*, 1998). Our finding that 23.5% of children admitted with CAP had evidence of *M. pneumoniae* infection concurs with these observations and evidence reported from elsewhere in the tropical region, namely Thailand (Liktinukul and Chirathawora, 1992), Singapore (Chong *et al*, 1997) and India (Chaudhry *et al*, 1998). However, in many areas in Malaysia and in the less developed nations of the tropics, laboratory support for serological diagnosis of *M. pneumoniae* infection is not readily available. In such instances, the clinician may have to initiate empirical treatment with macrolides for children considered having *M. pneumoniae* infection. Identifying children with *M. pneumoniae* infection is not always easy, as there are no definitive specific symptoms and signs. Nonetheless, our observations suggest that children admitted with CAP who are above the age of 3 years, are Chinese, have an illness duration of more than 7 days and have peri-hilar infiltrates on the chest X-ray are more likely to have *M. pneumoniae* infection. These features can at least provide a guide to clinicians in Malaysia in identifying the group of children who will most likely benefit with macrolide therapy. It was nonetheless surprising to find an ethnic predisposition of Chinese children for *M. pneumoniae* infection. Whether this observation is a reflection of genetic predisposition or the influence of the individual ethnic sociocultural environment remains unanswered. Chinese families in Malaysia are more likely to enroll their children in childcare facilities at an earlier age as both parents work, providing the means of exposure for transmission of respiratory infections. The prevalence of *M. pneumoniae* infection in children with CAP in Chinese predominant nations of this region is reported to be about 30% (Chay *et al*, 1992). In this study, 22 out of 51 (43.1%) of Chinese children with CAP were sero-positive for *M. pneumoniae* compared to 13.8% Malay and 18.8% Indian children (Table 2).

Severe extra-pulmonary complications were uncommon in our study population although life threatening complications especially cardiac (Ponka, 1979) and neurological dysfunction (Lerer and Kavarsky, 1973) can occur in 5 - 10% of cases. All but one of the children admitted with *M. pneumoniae* infection were discharged well after treatment with macrolides.

The study design did not take into account the importance and infective contribution of other causative organisms apart from *M. pneumoniae*. Clearly, mixed infections with especially bacterial organisms would require a different approach in patient management and selection of antibiotics for treatment. However, mixed infections with respiratory viruses or other bacterial organisms are not common with *M. pneumoniae* (Juven *et al*, 2000). In addition, the detection rate of respiratory viruses by immunofluorescence in our study population was not significantly different among *M. pneumoniae* sero-positive and sero-negative children.

Our observations here reiterate the importance of *M. pneumoniae* infection in children with CAP in Malaysia. The use of macrolide antibiotics should be considered in a good proportion of children admitted with CAP by taking into account the clinical parameters described here.

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