RESEARCH PAPER

Bacterial Co-infection in Hospitalized Children with *Mycoplasma pneumoniae* Pneumonia

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Objective: To describe the frequency and impact of bacterial co-infections in children hospitalized with *Mycoplasma pneumoniae* pneumonia.

Design: Retrospective, descriptive study.

Setting: Tertiary-care hospital in Beijing, China.

Participants: 8612 children admitted to Beijing Children's Hospital from June 2006 to June 2014.

Methods: According to the testing results of etiology we divided the cases into pure *M. pneumoniae* infection group and mixed bacterial infection group. We analyzed clinical features, hospital expenses and differences between these two groups.

Results: 173 (2%) of included children had bacterial co-infection. 56.2% of bacterial pathogens were identified as *Streptococcus pneumoniae*.

Conclusion: The most common bacterium causing co-infection in children with *M. pneumoniae* pneumonia was *S. pneumoniae*.

Keywords: *Acute respiratory infection, Etiology, Microbiology, Streptococcus pneumoniae.*

Mycoplasma pneumoniae is a common cause of community-acquired pneumonia (CAP) in children [1,2]. There is a scarcity of studies investigating co-infections of *M. pneumoniae* pneumonia (MPP) in children. The purpose of this study was to investigate the frequency and impact of bacterial co-infection in hospitalized children with MPP. Bacterial co-infection occur in respiratory MPP infections, but the attack rates and the clinical profile are not clear. The purpose of this study was to investigate the impact of bacterial co-infection in hospitalized children with MPP.

METHODS

Medical records of all patients with MPP who were admitted to Beijing Children's Hospital from June 2006 to June 2014 were reviewed. The Pediatric Internal Medicine Department had 10039 MPP admissions during this time. Cases were eligible for enrolment if complete data were available. Pneumonia was diagnosed according to standard guidelines [3-5].

Patients were excluded if they had chronic pneumonia [6], tuberculosis (TB), fungal, Epstein-Barr virus (EBV) or Cytomegalovirus (CMV) infection, congenital immuno-deficiency, malignancy, or were receiving immuno-suppressant agents. A total of 8,612 children aged 0-17 years old were included in this analysis (***Fig.* 1**).

The acute and convalescent serum were obtained and measured for antibody response to *M. pneumoniae* by enzyme-linked immunosorbent assay methods (Serodia-mycoii, Japan) [7]. An acute infection was indicated by a 1:160 antibody titres [8]. Patients were also evaluated for viral, bacterial, tubercular or fungal infections.

All patients were screened for pulmonary tuberculosis by the Purified protein derivative skin test with 5TU purified protein derivative. Blood, pleural effusion and bronchoalveolar lavage fluid (BAL) were sent for slide review and bacterial, *M. tuberculosis* and fungal culture.

A case with a co-infection was defined as any bacterial pathogen except *M. pneumoniae* detected in any specimen. A patient was considered to have a single infection if *M. pneumoniae* was the only pathogen detected.

The severity of pneumonia was assessed by scores from 0 to 5 according to the number of following clinical findings observed in the patients during admission (***Table* I**): fever (>38.5º), rapid breathing (and/or lower chest wall indrawing), decreased oxygen saturation breathing room

air (<92%), more than 7 days of hospital stay, more than 2 affected pulmonary lobes on chest *X*-rays. The patients with severity score ≥3 were defined as severe pneumonia group and ≤2 as non-severe pneumonia group [5].

The management of CAP in infants and children was done as per standard guidelines [3-5]. Patients with severe *M. pneumoniae* pneumonia who required intensive care unit (ICU) admission were defined as per Infectious Diseases Society of America/American Thoracic Society criteria for severe CAP [9]. The symptoms mentioned above were typical of severe *M. pneumoniae* pneumonia.

Statistical analyses: Analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL). The differences in age distributions among patients with various pathogens identified were tested by an independent sample t-test. $P<0.05$ was considered statistically significant. Parametric data were compared with independent sample t-tests. Categorical data were analyzed by using the chi-square test. We have performed a univariate and multivariate Cox's regression analysis for various factors affecting hospital stay more than 7 days.

RESULTS

A total of 8612 children (age 2 m - 17 y; 51.6% males) hospitalized with MPP were included in the study. Characteristics of the 8,612 children hospitalized with MPP are shown in ***Table* II**. There were 1012 children with severe pneumonia; and their hospital stay was longer

Tests for bacterial, acid-fast bacilli and fungal infections were performed in all patients, and 2% (173/8612) of cases were positive for at least one bacterial pathogen in addition to *M. pneumoniae*. Bacterial isolates in these 173 cases are listed in ***Table* III**. One bacterial pathogen was identified in 93.1% (173/185), and two bacterial pathogens were identified in 6.9%(12/173). *S. pneumonia*, Haemophilus influenzae (*H. influenzae*) and Staphylococcus aureus (*S.aureus*) were the most common source of infection (***Table* III**).

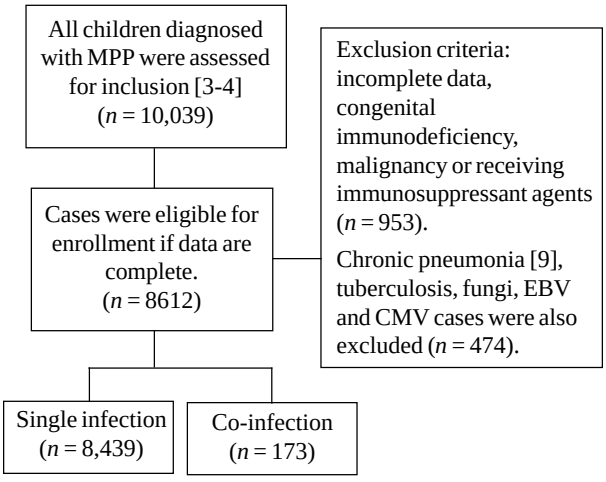

FIG. 1 *Study flow chart.*

Significant differences were observed in course of diseases, leukocyte count, and C-reactive protein between single and co-infections (***Table* II**). There was no significant difference in Neutrophil, Lymphocyte, Platelet, Serum lactate dehydrogenase (LDH), Serum Creatine kinase (CK) and Serum Alanine amino-transferase (ALT) between patients with single infections and those who with co-infection (***Table* II**). Hospital stay of children with single infections was shorter as compared to those with than bacterial co-infections (***Table* II**).

***Web Table* I** presents the results of univariate and multivariate Cox's regression analysis for various factors affecting hospital stay more than 7 days. Age was an important factor affecting hospital stay. Unilobar or Multilobar pneumonia was another important factors. Mixed infections and severe pneumonia also contributed to prolonged hospital stay

DISCUSSION

In this retrospective study from China, 2% of children with MPP were infected with another bacterial pathogen.

TABLE I SEVERITY ASSESSMENT OF PNEUMONIA IN INCLUDED CHILDREN

	Mild	*Severe*
Infants	Temperature <38.5ºC	Temperature<38.5ºC
	RR<50/min	RR>70/min
	Mild recession	Moderate to severe recession
		Nasal flaring
		Cyanosis
		Intermittent apnoea
		Grunting respiration
	Taking full feeds	Not feeding
Older children	Temperature <38.5ºC	Temperature<38.5ºC
	RR<50/min	RR>50/min
	Mild breathlessness	Severe difficulty in breathing
		Nasal flaring
		Cyanosis
		Grunting respiration
	No vomiting	Signs of dehydration

RR: respiratory rate.

TABLE II CLINICAL CHARACTERISTICS OF CHILDREN HOSPITALIZED WITH *M. PNEUMONIAE* PNEUMONIA

Characteristic	*Single infection*	*Co-infection*	*P value*
Number	8439	138	
Females; No.(%)	4091(48.5)	54	
Age (year)	9.2	5.9	0.001
Course of disease (d)	8.3	12.6	0.003
Laboratory findings			
Leukocyte count ($\times 10^9$/L)	6.21	12.1	0.001
Neutrophil (%)	71.2	65.8	0.122
Lymphocyte (%)	15.6	17.4	0.416
Platelet ($\times 10^9$/L)	134.0	140.8	0.856
C-reactive protein (mg/L)	22.1	31.6	0.006
Serum LDH (U/L)	326.2	323.9	0.561
Serum CK (U/L)	33.2	34.2	0.082
Serum ALT	61.0	62.9	0.091
Hospital stay, median	8.9	14.2	0.001

S. pneumoniae was the leading cause of bacterial co-infection. Co-infections led to more disease severity in children with MPP compared with single infections.

There were several limitations to our study. First, nearly all children in our study received antibiotic treatment. This may have affected the results of bacterial culture. Second, we did not study co-infection with viruses.

Frequency of co-infections in our study was lesser than that seen in few other reports from China [10,11]. This could be related to inclusion of viruses as cause of co-infectioin in these studies. The distribution and age categorization of various bactria isolated in our study is in general similar to other reports from developing countries [12,13].

We conclude that bacterial co-infections are relatively uncommon in *M. pneumoniae* pneumonia. *S. pneumoniae* is the most common cause of bacterial infection in *M. pneumoniae* pneumonia.

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TABLE III PATHOGENS INDENTIFIED IN CHILDREN WITH MYCOPLASMAL PNEUMONIA

Pathogen(s)	*Cases*	*Pathogen(s)*	*Cases*
S. pneumoniae + H. influenzae	3	*S. epidermidis*	2
S. pneumoniae + K. pneumoniae	1	*S. aureus*	12
S. pneumoniae + B. cepacia	3	*B. cepacia*	4
S. pneumoniae + H. parainfluenzae	3	*Sewer coli*	1
B. cepacia + H. influenzae	1	*M. luteus*	1
A. baumannii + S. coli	1	*P. aeruginosa*	7
S. pneumoniae	94	*N. gonorrhoeae*	4
H. influenzae	19	*E. coli*	1
H. parainfluenzae	10	*A. baumannii*	2
K. pneumoniae	4		

WHAT THIS STUDY ADDS?

- About 2% of children with *Myloplasma pneumoniae* pneumonia may have bacterial co-infection.

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WEB TABLE I MULTIVARIATE COX'S REGRESSION ANALYSIS FOR VARIOUS FACTORS AFFECTING HOSPITAL STAY >7 DAYS

Facters	*B*	*P*	*RR*
Age	0.241	0.046	0.786
Gender	0.101	0.571	1.107
Severity of pneumonia	0.249	0.031	0.780
Unilobar or Multilobar pneumonia	0.644	0.000	1.903
Hypoxia	8.455	0.934	0.000
Hypercapnia	8.426	0.901	0.000
Electrolyte disturbances	6.356	0.982	0.002
Organ involvement other than lung	0.213	0.761	0.808
Co-infections with MPP	0.612	0.029	1.595
Cephalosporin antibiotics	0.668	0.465	1.590
Azithromycin	7.950	0.963	0.000
Prolonged hospital admission	0.478	0.420	0.620
Nutrition	0.109	0.927	0.897
Duration of disease before hospital admission	0.087	0.054	1.090
Other co-morbid conditions	0.194	0.277	1.214