

Status of *Mycoplasma pneumoniae* Pneumonia in Chinese Children: A Systematic Review

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Abstract

Mycoplasma pneumoniae pneumonia (MPP) becomes one of the most important health problems in China recently. Data for MPP in China is scarce. Although macrolides and/or corticosteroids had been reported to be effective treatment for MPP, the long-term outcome remained uncertain. A study on status of MPP in China was conducted via a systematic review of published studies which have the Chinese data and collected from published PubMed and core journals of China Knowledge Resource Integrated Database (CNKI). The analysis was based on epidemiology, clinical characteristics, treatment, drug resistance and prognosis. Twenty five articles concerned about MPP in Chinese children and adolescent were enrolled, including 11 studies on epidemiology/etiology, 11 studies on clinical characteristics, 7 studies on drug resistance, 5 studies on treatment from mainland China respectively. The overall incidence of MPP ranged from 7.1% to 54.4%. Fever and cough were most frequently identified in manifestations. Drug resistance to macrolides ranged from 18.9% to 90%. The outcome of treatment in patients who received combined treatment of macrolides, cephalosporin antibiotics and/or corticosteroid seems to be better than those who received macrolides only. Macrolide combined with cephalosporin or corticosteroid both may decrease the severity of MPP in the past decade. There was not enough evidence to suggest that corticosteroid can decrease the mortality of MPP in children. And a multi-center, randomized double blind research on the effect of corticosteroid was encouraged.

Keywords

Mycoplasma pneumoniae, Pneumonia, Chinese Children, Systematic Review

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1. Introduction

Mycoplasma pneumoniae (MP) is among the smallest microorganisms which is capable of self-replication, with a whole genome [1]. MP is a frequent cause of community acquired pneumonia (CAP) in children, which has been well described and is considered self-limited in most cases. When it adheres to human airway epithelial cells, MP can trigger a series of immunological responses, which result in both atypical respiratory tract symptoms (e.g. fever, cough, headache, sore throat, runny nose, general malaise) and various extra-pulmonary complications such as encephalitis, meningoencephalitis, Guillain-Barre syndrome, optic neuritis, nephritis, rash, arthritis, and pericarditis [2]. However, the number of severe cases and pulmonary complications appears to be increasing in recent years.

CAP is the main cause of hospitalization and death of children in China, especially for children 5 years old and younger. Although many studies have focused on etiologies of pneumonia, there are limited high quality data regarding MPP in China. The positive rates of MP infection range from 10% - 30%, and may reach 50% - 80% in years of peak incidence or during local outbreaks. Global pandemics of MP generally occur every 3 - 7 years, and may persist for 1 - 2 years [3] [4]. Because MP lacks a cell wall, it is not susceptible to penicillins and other β -lactam antibiotics. However, drug resistance to the macrolides has been observed in *Mycoplasma pneumoniae* strains and appears to have been increasing in China and other area all over the world since year 2000. Improving the therapeutic management of pneumonia has been defined by international experts as one of the top priorities to decrease the CAP burden and improve health worldwide [5].

The present study was designed using a systematic review on the status of MPP patients in Chinese children, including the epidemiology, clinical characteristics, treatment, drug resistance and prognosis. Overall, the present study may provide a whole view on MP infection in large Chinese pediatric population.

2. Methods

2.1. Published Paper Review

In March 2014, a PubMed software was used to search Medline and core journals of China Knowledge Resource Integrated Database (CNKI) (Library of the Capital Medicine University, Beijing, China) using the following search terms and relative Chinese words: “*Mycoplasma pneumoniae* pneumonia”, “*Mycoplasma pneumoniae*”, “China”, “Chinese children”. We also searched the Google scholar database (restricting the search on papers published since 2000), the World Health Organization online libraries [6] [7]. The references’ list of eligible papers and directly contacted their authors were also conducted. The EMBASE database was searched to complete the review, using the key words “community acquired pneumonia” (epidemiology and etiology, clinical characteristics, drug resistance, prognosis). Furthermore, we excluded animal studies, studies performed beyond Chinese mainland or mainly located in adjacent area, case reports and studies not focusing on pneumonia. References on hospital-acquired infections, on pulmonary TB or CAP in immunocompromised patients were excluded. Finally, we excluded studies presenting only virologic, immunologic or genetic results on MP pneumonia and studies conducted prior to year 2000. Data were extracted in duplicate using a pre-defined data sheet.

2.2. Risk of Bias and Data Analysis

Descriptive statistics were computed using SPSS 13.0 for windows software (Integral Solutions Limited, USA). The following data were abstracted as available: first author, year of publication, study period, sample size, MPP prevalence, main therapeutic regimens, prognosis or pulmonary complications.

Drug resistance data is documented as each studies’ authors and the tests and interpretative breakpoints they used. Results are presented as numeric tables presenting frequencies and narrative analysis.

3. Results

Screening process of studies is outlined in **Figure 1**. A total of 96 papers were found by their titles and whole contents reviewed for relevance in PubMed, Google Scholar, WHO and EMBASE data, and 303 papers in CNKI. Only 25 studies met the inclusion criteria, most of them were published in 5 years.

The characteristics for each study are presented in **Table 1**. The etiologies of CAP were determined by antigen and serological tests, or molecular diagnostic tools (PCR and Real Time-PCR).

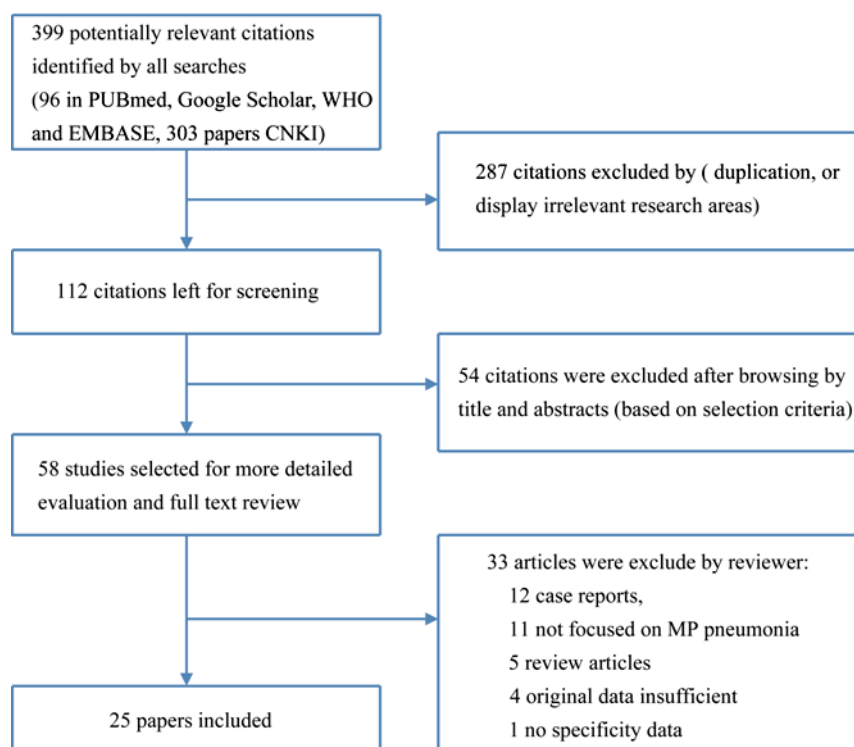


Figure 1. Study screening scheme.

In 11 papers concerned about epidemiology/etiology, the overall incidence of MPP ranged from 7.1% [9] to 54.4% [22]. The incidence seems increased in recent years, particularly in East Asia. Data from several studies showed that the prevalence of MP infection was higher during fall, winter, and spring, and lower in summer. Fever and cough were most frequently identified in clinics, followed by wheezing and other lung abnormalities. Of particular note is the airway mucosal damage, in some severe cases, it is the risk factor for atelectasis and obstructive bronchitis [32]. MPP can cause multi-system infections in children, and may be accompanied with other pathogens. The positive rate of pneumonia diagnosed by X-ray was not significantly different between children with MP infection and those with other pathogen infection [10]. In most cases of MPP, the leukocyte count, neutrophil proportion, CRP, and ESR were normal or only slightly elevated. Drug resistance rate vary from 18.9% [13] to 90% [8], may contributed to the different test methods and interpretative breakpoints. Gene mutations associated with macrolides resistance were very common. Several point mutations in 23S rRNA have been reported, and different mutations cause different level of resistance to 14-, 15-, and 16-member macrolides. No death case was reported in all studies, but in younger children, the complications are more often to be seen and some of them had severe clinical course [29] [30].

4. Discussion

Our study findings indicate that pathogens isolated in patients with CAP in China seem to differ from those described from Western countries. *Streptococcus pneumoniae* remains the most important pathogen in adults of all ages admitted to hospital with CAP [33], and the fulminant MPP cases were rarely reported in Japan (only 52 fulminant MPP cases were reported between September, 1979 and February, 2010) [34]. In the last ten years, great emphasis has been placed on the role of MP infection with atypical pneumonia in children. The incidence of MP infection in CAP may be higher than previously thought [22]. But in MP infection, it is difficult to set up a criteria list for the “gold standard” to detect acute or remote infections. As to different studies, various etiologic tests have been used. Currently, the laboratory diagnosis of MP infection is mainly based on the serologic or molecular-based testing. Compared with serological index, PCR results seemed to be the most promising direct technology due to its high sensitivity and specificity [35] [36]. There needs an universally agreed-upon gold standard assay for detecting MP now.

Table 1. Main characteristics of studies on MPP in Chinese children.

First author	Published year	Study period	Patients number	MP infection ratio	Chief symptoms	Main treatment regimens	Drug resistance ratio	Prognosis or pulmonary complication
Yang Liu [8]	2010	2008-2009	100	N/A	N/A	N/A	90%	N/A
Gang Liu [9]	2005	1998-1999	85	7.10%	fever, tachypnea, cough	N/A	N/A	N/A
X. Y. He [10]	2013	2008-2010	12025	20.23	N/A	N/A	N/A	N/A
Bin Cao [11]	2010	2008-2009	215	29.30%	N/A	N/A	69%	N/A
Z. Y. Ou [12]	2008	1998-2005	173	78.03%	N/A	N/A	N/A	N/A
A. M. Yang [13]	2013	2010-2011	3529	29.07%	N/A	N/A	18.91%	N/A
Deli Xin [14]	2009	2003-2006	370	N/A	N/A	N/A	92%	N/A
Yue Jiang [15]	2013	2011-2011	205	28.80%	N/A	N/A	84.40%	N/A
A. Z. Lu [16]	2011	2007-2009	614	N/A	Fever, cough, abnormal breath sounds	Azithromycin and third generation of cephalosporins Plus Corticosteroids	N/A	Clinically improved 5 had pleural effusions
Q. L. Zhang [17]	2013	2007-2010	707	11% among severe CAP	cough, retractions and fever	N/A	N/A	Young age and underlying congenital heart disease were risk factor with PICU support
H. Q. Zhao [18]	2014	2007-2012	3073	19.13%	N/A	N/A	90.70%	N/A
S. N. Cui [19]	2012	2007-2010	84	N/A	N/A	combination therapy (azithromycin and ceftriaxone) vs single (azithromycin)	N/A	Overall response rate 84.13% vs 57.14%
X. X. Wu [20]	2013	2011-2012	92	N/A	cough, fever, chest pain	azithromycin vs erythromycin	N/A	Effective rate 93.48% vs 67.39%
X. J. Wu [21]	2014	2011-2012	68	N/A	N/A	azithromycin vs erythromycin	N/A	Effective rate 91.18% vs 67.65%
Tao Zhang [22]	2014	2011-2013	792	54.40%	N/A	N/A	59.10%	N/A
X. Q. Sun [23]	2013	2010-2012	216	N/A	fever (83.33%), cough (90.74%), wheeze (33.16)	N/A	N/A	Complication: digestive (34.72%), urinary (28.24), rash (6.94%), Neurology (6.94%)
Y. M. Zhang [24]	2010	2006-2007	166	N/A	N/A	N/A	N/A	Pulmonary atelectasis (10.03%)
Hui Gao [25]	2013	2007-2010	875	N/A	N/A	N/A	N/A	Risk factor for complication: long fever course, MOD, large pleural effusion, located right upper lung
Z. T. Tan [26]	2013	2011-2012	310	N/A	fever, cough, wheezing	N/A	N/A	N/A

Continued

L. Q. Ke [27]	2013	2011-2012	3156	13.53%	N/A	N/A	N/A	N/A
Y. C. Xu [28]	2011	2007-2009	14799	18.50%	N/A	N/A	N/A	N/A
X. Y. Liu [29]	2013	2010-2012	46*	N/A	rapid progress, more complication, delayed positive for Ab, wheezing and rales	N/A	N/A	N/A
L. X. Ren [30]	2013	2010-2012	96*	N/A	Fever (80.2%), cough (100%), wheezing (55.2%), shortness of breath (33.3%)	azithromycin	N/A	71.9% patients have one or more complication
Xian Shi [31]	2014	2011-2012	190	N/A	Fever (92.63%), dry cough (86.84%)	N/A	N/A	Complications: digestive (25.79%)
A. X. Jiao [32]	2010	2006-2007	144	N/A	Airway mucosal follicular, Hyperplasia, mucus secretion	N/A	N/A	N/A

*less than 3 years old patients.

According to the results of our study, MPP is very common in present society, but its clinical features and laboratory parameters are not clear and specific. In the majority of investigated cases of MP infections, the leukocyte count, neutrophil proportion, CRP, and ESR were normal or only slightly elevated [10]. Although some minor variations maybe detected, there was no statistically significant of the peripheral leukocyte, CRP, and ESR value between the children with MPP and those with other viral infections. Therefore, the routine laboratory tests are not specific to diagnose children with MP infection. In some severe cases, the airway mucosal damage is the risk factor for atelectasis and obstructive bronchitis, contribute to prolonged pneumonia. This phenomenon has been increasingly recognized by pediatricians in recent years. So airway mucosal damage under bronchofiberscopy may be a promising method to diagnose MPP [32]. In children, MPP may be complicated by plastic bronchitis, even if it did not have severe systemic inflammatory reaction. In present study, we found the presence of fever, cough and wheezing seemed to be peculiar to the diagnosis for MPP. Thus, it may be not possible to predict the occurrence of MPP by depending only on the initial clinical symptoms and common laboratory parameters. MPP can cause multi-system infections in children, and may be accompanied with viral infections, school-age children are more susceptible to this disease, particularly in autumn and winter [18]. So, it is essential for identifying the respiratory infection pathogen. And the antibiotic treatment should be based on the results of etiologic tests.

In present study, the macrolide resistance rates were very high in China, up to 90% [8]. Macrolide resistance in *M. pneumoniae* is due to mutations in 23S rRNA [37]. Several point mutations in 23S rRNA have been reported, and different mutations cause different level of resistance to 14-, 15-, and 16-member macrolides. Furthermore, a number of adhesion genes, including P1, P30, and P116, have been investigated in the adhesive mechanism of MP and explored for diagnostic purposes [10]. The variety of drug resistance may contribute to different areas. Though the macrolides resistance in MPP is quite high in China, macrolides and cephalosporin antibiotics are still the most common drugs used in the treatment of MPP in children. The reason may be that MPP always have concurrent infections. The impact of the resistance to macrolides on the efficacy of treatment with macrolides is thus needed to be investigated.

As in Zhang's study, young age and underlying congenital heart disease were risk factor with severe CAP for PICU support, among them 11% were severe type of MPP [17]. And long fever course, MOD, large pleural effusion, located right upper lung were the risk factor for severe complications [25]. Infantile patients may have more rapid clinical progression and complications [29]. It has been proposed that cell-mediated immunity play an important role in the progress of MP infection [38]. Thus immune suppressive therapy would be useful. Because corticosteroids have roles of immune regulation and anti-inflammation, it was reported that corticosteroids

could improve symptoms and pulmonary lesion rapidly in children with MPP [39] [40]. However, there was no evidence-based report about appropriate use of cortical steroid, in particular, those of dosage, administration route, or duration of treatment [16]. All these reports were cases based and the severity of diseases were different, further controlled double-blind studies to define the optimal methods for corticosteroid use in MP may be necessary.

The results of our study could contribute to better understanding of the epidemiology, clinical, and laboratory characteristics of MPP in Chinese pediatric population. Future studies are encouraged to improve the lab techniques for detecting MP rapidly and specifically, and more multi-center double blind control studies on treatment for MP infection.

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Note List about the Abbreviations

MP: *Mycoplasma pneumoniae*;
MPP: *Mycoplasma pneumoniae* pneumonia;
CAP: Community acquired pneumonia;
CNKI: China Knowledge Resource Integrated Database;
TB: Tubercule bacillus;
CRP: C-reactive protein;
ESR: Erythrocyte sedimentation rate;
rRNA: ribosomal ribonucleic acid.

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