

# Epidemiology and clinical characteristics of pathogens responsible for the hospitalization of children with segmental/lobar pattern pneumonia

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## Research article

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## Abstract

**Backgrounds** The occurrence of segmental/lobar pattern pneumonia (S/L-PP) in children increases with years. The pathogens of the disease may change for the abuse of antibiotics and the application of vaccines. Therefore, pathogens of S/L-PP in hospitalized children and their association with clinical characteristics may have changed. **Objective:** To analyze the pathogens of S/L-PP in hospitalized children and their association with clinical characteristics. **Methods:** The current study analyzed the epidemiological and clinical characteristics of pathogens in children with S/L-PP at a single hospital between 1st Jan 2014 and 31st Dec 2018 retrospectively. The pathogens and their associations with clinical characteristics were statistically analyzed. **Results:** A total of 593 children with S/L-PP received treatment at a single hospital during the study period by inclusion criteria. 451 patients were single positive for one pathogen and 83 patients had multiple infections. *Mycoplasma pneumoniae* (*M.pneumoniae*) (72.34%) was the most commonly detected pathogen, followed by *streptococcus pneumoniae* (*S.pneumoniae*) (8.77%). The infection of *M.pneumoniae* in children with S/L-PP increased with years ( $p<0.05$ ). The positive rate of *M.pneumoniae* increased with ages of patients ( $p<0.05$ ). *M.pneumoniae* was statistically associated to the extrapulmonary manifestations while *S.pneumoniae* was statistically associated with abnormal white blood cells (WBCs) and C reactive proteins (CRPs) ( $p<0.05$ ). **Conclusion:** *M.pneumoniae* was the most positive pathogen in children with S/L-PP. The positive rate of *M.pneumoniae* in children with S/L-PP increased with years and the ages of children. *M.pneumoniae* was associated with extrapulmonary manifestations while *S.pneumoniae* was associated with abnormal WBCs and CRPs.

## Introduction

Community-acquired pneumonia (CAP) is one of the most common respiratory disorders in children, which often needs hospitalization [1]. S/L-PP in children is one of the common CAPs based on chest radiological findings of consolidation. Patients with S/L-PP often suffer from cough, fever, and even serious complications such as pulmonary atelectasis, pulmonary consolidation, pulmonary necrosis and respiratory failure, increasing the rate of morbidity, mortality as well as the cost of health care. However, the pathogen profile of S/L-PP in children has not been ever reported and they may vary with regions, times, antibiotics use, vaccines and et al. The detection of pathogens often needs several hours or even days. Clinical doctors have to treat patients with antibiotics on experiences usually. The improper use of antibiotics may prolong the suffering of patients and cause more sequelae. So it was important to figure out the pathogen profile of S/L-PP in children and their associations with clinical characteristics.

The occurrence of S/L-PP in children increases with years clinically and has drawn the great attention of patients and doctors. In this research, the pathogens of S/L-PP and their clinical characteristics were retrospectively analyzed in hospitalized children who were admitted to Zibo Central Hospital during 1<sup>st</sup> Jan 2014 and 31<sup>st</sup> Dec 2018 as follows.

## Patients And Methods

**Patients.** Zibo Central Hospital is situated in the central of Shandong Province in China. The hospital serves as a primary source of healthcare for people in Zibo area, which provides about six million people with common economic development and stable infrastructure. In the study, the medical records of children with pneumonia (as defined by the specifications in the International Classification of Diseases, 10<sup>th</sup> edition, ICD-10 code) who were admitted to Zibo Central Hospital between 1<sup>st</sup> Jan 2014 and 31<sup>st</sup> Dec 2018 was retrospective analyzed.

The pneumonia pattern was characterized according to the World Health Organization Standardization of Interpretation of Chest Radiographs for the diagnosis of CAP in children [2]. Patients were included by the inclusion criteria: 1) Patients had a chest radiograph performed during hospitalization; 2) Patients had a serological test of pathogens detected  $\geq 7$  days following the onset of the disease. Patients were excluded according the exclusion criteria: 1) Patients  $>14$  years of age; 2) Patients suffering from known coexisting chronic, progressive or oncological illnesses; 3) Patients had a chest radiograph of pulmonary perihilar linear opacities or reticulonodular infiltrates.

During the study period, a total of 9342 patients visited the hospital and 593 patients with S/L-PP were included in this study. Data including gender, age, clinical signs and symptoms, complication, laboratory and radiological findings, and duration of hospitalization were collected. Microbial cultivation was carried out by culturing and processing with blood or sputum specimens in accordance with standard microbiological procedures. Indirect immunofluorescence was used to detect *M. pneumoniae*, respiratory syncytial virus (RSV), chlamydia pneumonia (CP), influenza A virus (IFA), parainfluenza virus (PIVS), adenovirus (ADV), Q fever Coxiella (COX), Legionella pneumophila (LP), and influenza B virus (IFB).

Statistical analysis.

The Statistical package for the Social Science for Windows version 11.5 (SPSS, Inc., Chicago, IL, USA) was used for Statistical analyses. Continuous variables are expressed as mean  $\pm$  standard deviation. For the age of patient may relate to the levels of certain laboratory indices such as erythrocyte sedimentation rate (ESR), white blood cell counts (WBCs) and C-reactive protein (CRP), they were transformed into categorical data (normal or abnormal). The categorical variables were assessed by the Chi-square test while the continuous variables were assessed by the method of t-test.  $P<0.05$  was indicated as a statistically significant difference.

## Results

Overview of patients

Of 9342 children hospitalized with pneumonia from 1<sup>st</sup> Jan 2014 to 31<sup>st</sup> Dec 2018, 593 patients with S/L-PP were enrolled in this study. Among them 398 patients were boys and the rest were girls. The male to female ratio was about 2:1. The age of the patients with S/L-PP ranged from 1 year to 13 years (7.4±3.1 years). The number of patients with S/L-PP each year was 86, 98, 115, 137, 157 respectively from 2014 to 2018. The annual incidence of S/L-PP increased with years over the study period (P<0.05). The duration of fever and cough were 4.6±2.1 days and 10.6±8.7 days respectively. 169 patients had a gasping and 208 patients had pulmonary crackles at onset. There were 149 patients with extrapulmonary manifestations including erythematous maculopapular rash, liver and kidney function lesions, and neurological complications. Only a few patients had pleural effusion. There were 383 patients with abnormal WBCs, 69 patients with abnormal ESR and 148 patients with abnormal CRP. The duration of hospital stay was 15.5±3.1 days.

#### Pathogen distribution with years

Table.1 summarized the distribution of pathogens with years including M. pneumoniae, RSV, CP, IFA, PIVS, ADV, COX, LP, IFB, S.pneumoniae, Staphylococcus aureus (S. aureus), Pseudomonas aeruginosa (Paeruginosa), Escherichia coli (E.coli), Klebsiella pneumoniae (K.pneumoniae), and so on, and showed the positive rate of M.pneumoniae increases with years. The number of patients infected by M.pneumoniae was 43, 67, 96, 106, and 117 respectively each year during the study period, and the positive rate of M.pneumoniae between the groups with years was significantly different (p<0.05). But no significant differences in the positive rate for other pathogens with years between the groups were found.

#### Age distribution of pathogens

Table.2 summarized the distribution of pathogens with age group and showed that the positive rate of M.pneumoniae increased with ages. Significant differences were observed in the positive rate of M.pneumoniae between the age groups. However, no significant differences were found in the positive rate of other pathogens between the age groups.

#### Sex distribution of pathogens

Significant differences were not observed for M. pneumoniae and S.pneumoniae between male patients and female patients. 18 patients were positive for IFB including 6 male patients and 12 female patients. Female patients displayed significantly higher positive rate for IFB. No significant sex difference was observed for the other pathogens.

#### Season distribution of pathogens

In general, the seasonality profile of each individual pathogen was diverse. However, we did not observe a distinct pattern for the pathogens.

#### Mixed infection types of pathogens

Co-infections with multiple pathogens were common. There were 91 patients in whom 2 or more pathogens were positive, representing 15.34% of the patients, and the types of co-infection were complex. These data indicated that 27.40% of the children with M.pneumoniae infections were co-infected with other pathogens. A total of 15 patients showed infection with 3 pathogens or more. (Table.3)

#### Association between pathogens and patients' demographic and clinical characteristics

Table.4 summarized the patients' demographic and clinical information found in association with pathogen infections. The patients groups were divided according to pathogens. Patients with co-infections of pathogens were excluded. Since the sample size was too small to obtain significance in some statistical analyses, only M. pneumoniae and S.pneumoniae were included in the statistical analyses. M.pneumoniae was statistically associated to the extrapulmonary manifestations. S.pneumoniae was statistically associated with abnormal WBCs and CRP. (Table.5)

## Discussion

S/L-PP is a common pediatric low respiratory tract infection [3], which is involved in the community-acquired pneumonias (CAP). The incidence of S/L-PP increased with years recently. The considerably serious clinical manifestations including hyperpyrexia, cough and expiratory dyspnea often result in extra pulmonary multi-system complications. Currently there were no standardized therapeutic strategies on pediatric S/L-PP[3]. Although new antibiotics are developed increasingly, no obvious fall in the morbidity and mortality of S/L-PP have been observed. Generally, the patients with S/L-PP often have more severe symptoms than those with no S/L-PP. S/L-PP was more closely related to severe manifestations, including pleural effusion, higher rates of fever, extrapulmonary manifestations, abnormal WBCs, abnormal CRP and bacterial co-infection, as well as longer durations of fever and hospitalization [4]. In our research, the duration of fever and hospitalization of the patients with S/L-PP were 4.6±2.1 days and 15.5±3.1 days, which were similar to the previous report [4]. However, the pathogens distribution of the disease and their association with clinical characteristics in children has not been ever found to be reported. The microbes are difficult to isolate in children with S/L-PP for the difficulties in sputum expectoration and low positive rate of blood culture [5]. Some detection may be positive about a week after the onset of the disease. Therefore, the treatment of the disease based on knowledge and experience is very important. This research described the pathogens and their association with clinical characteristics in the patients with S/L-PP, which can add knowledge and experience of the disease for clinical doctors to treat it.

The positive rate of the pathogens in patients with S/L-PP was highly diverse in this research. M. pneumoniae was the most commonly detected pathogen. The total positive rate of M. pneumoniae was 72.34% (429/593). It increased with years, which suggested M. pneumoniae has become the main pathogen of the disease. This was different from the previous report [6-7]. In fact, it is estimated that M. pneumoniae infection is accountable for up

to 30-40% of CAP [8-11]. The classical radiological manifestations of *M. pneumoniae* pneumonia include segmental/lobar air-space consolidation, diffuse tiny centrilobular nodules and bronchovascular thickening [12-15]. The S/L-PP is considered to account for 17-76.5% of pediatric *M. pneumoniae* pneumonia cases. The incidence of S/L-PP shown an increasing trend [16-19]. So *M. pneumoniae* has drawn the great attention of clinical doctors and patients. However, there has been no any type of vaccines approved for use against *M. pneumoniae* now [20]. The positive rate of *M. pneumoniae* in patients with S/L-PP increased with ages of children. It was postulated with 2 explanations. First, old patients prefer social activity in herd and chances for them to be infected were high. Second, the progression of the immune system in the patients was different between old patients and young ones. A report suggested that *M. pneumoniae* pneumonia was closely correlated with the immune system of the patients [20]. The different progression state of the immune system between old patients and young ones may be related with the different positive rate of *M. pneumoniae* in the patients. The positive rate of *M. pneumoniae* in male patients was not statistically different from female ones, which suggested that *M. pneumoniae* infection was not affected by sex ratio. The patients with S/L-PP infected by *M. pneumoniae* occurred all the year round and didn't vary with the change of seasons. The extrapulmonary complications in patients with S/L-PP infected by *M. pneumoniae* were common and the prevalence of this kind of complication may be up to 26.17 % [4], which was similar to the results in this research. However the complications occurred few in patients infected by other pathogens and was not discussed in the research.

The second positive rate of pathogen in patients with S/L-PP was *S.pneumoniae* and it was 8% in the research. The positive rate of *S.pneumoniae* was much lower than that of *M. pneumoniae*, which was different from the previous understanding [6-7]. It was associated with the wide application of *S.pneumoniae* vaccines in China, which can prohibit the prevalence of *S.pneumoniae* infection [21-24]. The abuse of antibiotics was common in the nation, which can also bring down the infection of *S.pneumoniae*. The microbial cultivation can bring false negative results in some samples. And samples were usually taken after the patients had taken oral or intravenous antibiotics. It was another reason for the low positive rate of *S.pneumoniae* in the study. Compared with other pathogens, *S.pneumoniae* was significantly associated with abnormal WBCs and CRP, which may be used for the determination of S/L-PP pathogens in clinical practice. However, *M.pneumoniae* and *S.pneumoniae* in children with lobar pneumonia counted for 81.1% of the pathogens in total, which was much higher than that reported by Saraya T[25]. Other pathogens had low positive rate in this research, which was not discussed here.

Some patients were infected by two or more pathogens in the research. Two pathogens co-infection type was the most common one. The common co-infection type of two pathogens was *M. pneumoniae* and *S.pneumoniae*. The co-infection of 3 pathogens or more was less. The association between co-infection of pathogens and their clinical characteristics were not further discussed here for small cases.

The study is also associated with some limitations. First, clinical data were collected from medical records retrospectively, and therefore there may have been some selection bias. Second, the sample size of some samples was not large enough to obtain significance in some statistical analyses. Third, some pathogens may not be found due to the limitation of the detection method.

In a summary, *M. pneumoniae* was the most important pathogen in the children with S/L-PP. The prevalence of *M. pneumoniae* infection increased with years and ages of children. Old patients are more prone to be infected by *M. pneumoniae*. *M. pneumoniae* was associated with extrapulmonary manifestation while *S.pneumoniae* was associated with abnormal WBCs and CRP.

## List Of Abbreviations

S/L-PP segmental/lobar pattern pneumonia

*M.pneumoniae* Mycoplasma pneumoniae

*S.pneumoniae* streptococcus pneumoniae

CAP Community-acquired pneumonia

WBCs white blood cells

CRPs C reactive proteins

RSV respiratory syncytial virus

CP chlamydia pneumonia

IFA influenza A virus

PIVS parainfluenza virus

ADV adenovirus

COX Q fever Coxiella

LP Legionella pneumophila

IFB influenza B virus

ESR erythrocyte sedimentation rate

S. aureus Staphylococcus aureus

Paeruginosa Pseudomonas aeruginosa

E.coli Escherichia coli

K.pneumoniae Klebsiella pneumoniae

## Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Zibo Central Hospital. Written informed consent was obtained from the guardians of the patients.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Li yuyun and Wang yanxia conceptualized the study. Li yuyun and Wang yanxia were responsible for data curation, formal analysis and wrote the original draft. Ma Iiji, Li ying, Zheng yanfei and Zhang xiaoyue were responsible for resources, supervision, validation and visualization. All authors read and approved the final manuscript.

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## Tables

Talbe.1. Pathogen distribution with years in patients with S/L-PP

year	2014	2015	2016	2017	2018	X2	p
n	86	98	115	137	157		
M.pneumoniae	43	67	96	106	117	31.46	<0.01
RSV	5	4	5	3	3	3.68	>0.05
CP	4	4	4	2	2	4.24	>0.05
IFA	4	1	3	3	2	3.76	>0.05
PIVS	6	5	5	6	4	2.76	>0.05
ADV	5	5	4	4	2	4.68	>0.05
COX	4	5	5	4	4	1.71	>0.05
LP	3	3	4	1	1	5.37	>0.05
IFB	4	4	2	4	3	2.54	>0.05
S.pneumoniae	11	10	10	11	10	3.22	>0.05

Talbe.2. Age distribution of pathogens in patients with S/L-PP

age	age<3year	3≤age≤6	6≤age≤9	9≤age≤14	X2	p
n	81	108	169	235		
M.pneumoniae	45	67	128	189	25.79	<0.01
RSV	5	4	5	6	2.56	>0.05
CP	2	5	2	7	3.10	>0.05
IFA	2	2	2	7	1.57	>0.05
PIVS	2	5	10	9	1.84	>0.05
ADV	6	2	7	4	7.44	>0.05
COX	3	3	6	11	0.81	>0.05
LP	2	3	2	5	1.01	>0.05
IFB	5	3	3	7	3.65	>0.05
S.pneumoniae	7	9	17	19	0.73	>0.05

Talbe.3. Mixed infection types of pathogens

Co-infection type	number
2 pathogens	76
M.pneumoniae +RSV	5
M.pneumoniae +CP	4
M.pneumoniae +IFA	4
M.pneumoniae +PIVS	7
M.pneumoniae +ADV	4
M.pneumoniae +COX	10
M.pneumoniae +LP	4
M.pneumoniae +IFB	6
M.pneumoniae + S.pneumoniae	20
M.pneumoniae + S. aureus	2
M.pneumoniae + K.pneumoniae	1
M.pneumoniae + E.coli	1
RSV+CP	1
RSV+ E.coli	1
CP+IFA	1
CP+PIVS	1
CP+ADV	1
CP+ S.pneumoniae	1
IFA+LP	1
COX+LP	1
3	14
M.pneumoniae +CP+ADV	1
RSV+LP+IFB	1
PIVS+ADV+COX	1
M.pneumoniae +PIVS+ADV	1
M.pneumoniae +CP+ S.pneumoniae	1
M.pneumoniae +RSV+LP	1
M.pneumoniae +CP+IFA	1
M.pneumoniae +ADV+IFB	1
M.pneumoniae +PIVS+COX	1
M.pneumoniae +LP+ S.pneumoniae	1
M.pneumoniae +IFA+ P.aeruginosa	1
M.pneumoniae +ADV+COX	1
M.pneumoniae +RSV+CP	1
M.pneumoniae +IFA+COX	1
4	1
M.pneumoniae +IFA+ADV+COX	1

Talbe.4.Association between pathogens and patients' demographic and clinical characteristics

variables	M.pneumoniae	RSV	CP	IFA	PIVS	ADV	COX	LP	IFB	S.pneumoniae
N	353	11	7	3	14	8	6	4	8	28
gender										
male	246	10	3	3	10	4	3	2	4	20
female	107	1	4	0	4	4	3	2	4	8
age	7.8±4.1	8.4±3.1	10.2±2.6	5.4±3.6	6.5±5.2	6.8±4.5	7.6±3.8	8.3±5.2	6.8±3.9	7.9±3.5
fever										
yes	302	8	5	3	10	7	4	3	6	21
no	51	3	2	0	4	1	2	1	2	7
Duration of fever(days)	4.9±2.8	5.7±3.2	3.5±2.6	4.3±3.2	3.8±2.3	4.5±1.9	5.6±2.4	4.1±2.6	4.7±2.6	4.5±2.4
Duration of cough(days)	10.2±6.2	8.6±5.8	13.6±6.5	10.3±6.9	11.8±9.3	8.9±4.3	10.1±6.8	8.2±4.3	9.4±7.6	11.3±6.4
gasping										
Yes	122	3	0	0	1	2	0	0	0	2
No	231	8	7	3	13	6	6	4	8	26
Pulmonary crackles at onset										
yes	120	3	2	0	4	2	2	1	3	9
no	233	8	5	3	10	6	4	3	5	19
Pleural effusion										
Yes	15	2	1	0	1	0	0	0	1	1
no	340	9	6	3	13	8	6	4	7	23
Extrapulmonary manifestations										
Yes	102	0	0	1	2	1	0	0	1	3
no	251	11	7	2	11	7	6	4	7	25
WBC										
abnormal	245	5	4	2	6	5	5	2	4	27
normal	108	6	3	1	6	3	4	2	4	1
ESR										
abnormal	36	1	2	0	1	1	0	1	2	3
normal	317	10	5	3	12	7	6	3	6	25
CRP										
abnormal	81	3	2	1	4	3	2	1	3	24
normal	272	8	5	2	8	5	4	3	5	4
Duration of hospitalization (days)	15.8±4.1	14.2±4.3	13.6±5.8	12.5±3.6	14.9±5.2	15.1±3.7	13.9±6.2	14.7±5.1	14.6±2.4	15.3±4.4

Talbe.5. Comparison between M.pneumoniae and S.pneumoniae with patients' demographic and clinical characteristics

variables	M.pneumoniae	S.pneumoniae	X2	p
N	353	28		
gender				
male	246	20	2.06	>0.05
female	107	8		
age	7.8±4.1	7.9±3.5	0.13	>0.05
fever				
yes	302	21		
no	51	7	1.5	>0.05
Duration of fever(days)	4.9±2.8	4.5±2.4	0.73	>0.05
Duration of cough(days)	10.2±6.2	11.3±6.4	0.90	>0.05
gasping				
Yes	122	2		
No	231	26	8.88	<0.01
Pulmonary crackles at onset				
yes	120	9		
no	233	19	0.05	>0.05
Pleural effusion				
Yes	15	1		
no	340	23	0.26	>0.05
Extrapulmonary manifestations				
Yes	102	3		
no	251	25	4.3	<0.05
WBC				
abnormal	245	27		
normal	108	1	9.28	<0.01
ESR				
abnormal	36	3		
normal	317	25	0.06	>0.05
CRP				
abnormal	81	24		
normal	272	4	51.2	<0.01
Duration of hospitalization (days)	15.8±4.1	15.3±4.4	0.62	>0.05