Clinical Features of Plastic Bronchitis Related to Respiratory Tract Infection in 269 Children

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Research Article

Keywords: plastic bronchitis, risk factors, fiberoptic bronchoscopy, mycoplasma

Posted Date: January 5th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1173905/v1>

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Abstract

Background. Plastic bronchitis (PB) is a pulmonary disease characterized by the formation of bronchial casts (BCs) that lead to airway blockage. The study aimed to investigate the clinical features of PB related to respiratory tract infection.

Methods. A retrospective analysis was performed on data collected over a 5-year period (from January 2015 to December 2019) on children with PB (n=269). The clinical manifestations, laboratory data, imaging findings and management, were investigated. The single fiberoptic bronchoscopy (FOB, n=144) and multiple-treatment groups (n=125) were compared.

Results. A total of 269 PB children were included with a mean age of 6.7 ± 2.8 years. The majority of cases (n=241, 89.6%) were diagnosed with *Mycoplasma pneumonia* (MP) infection. The mean duration of fever and hospitalization was 10.6 ± 3.7 and 9.3 ± 3.2 days, respectively. All patients presented with cough and fever, 62 (23.0%) suffered from hypoxemia, and 144 (53.5%) had extrapulmonary complications. Higher levels of ESR, CRP, PCT, IL-6, LA, LDH, FER and D-dimer were observed. CT findings, including pulmonary consolidation, segmental or lobar atelectasis, pleural effusion and pleural thickening, were observed in 97.4%, 46.5%, 47.9% and 63.2% of cases, respectively. Furthermore, multivariate logistic regression analysis showed that N% >75.5%, LDH >598.5U/L, and D-dimer >1.2mg/L were independent risk factors for multiple therapeutic FOB.

Conclusions. MP is a major pathogen responsible for PB in children. Patients with PB are more likely to experience persistent fever and excessive inflammation and have severe radiological findings. FOB is an effective treatment for patients with PB, and children may require multiple FOBs for cast removal. N% >75.5%, LDH >598.5U/L and D-dimer > 1.2mg/L are independent predictors of multiple FOB treatment.

1. Introduction

Plastic bronchitis (PB) is an uncommon pulmonary disease characterized by the formation of bronchial casts (BCs) in the airways, which can partially or completely obstruct the tracheobronchial tree[1]. PB has been reported in children with surgically palliated congenital heart disease for the past decade, especially after the Fontan procedure[2]. With the wide application of fiberoptic bronchoscopy (FOB) in bronchopulmonary disease, accumulating evidence indicates that PB could be triggered by common pathogens in respiratory tract infection, including influenza virus (A and B), adenovirus (ADV) and *Mycoplasma pneumoniae* (MP) [3–7], suggesting that PB may not be a rare disease.

The main persistent symptoms of PB include recurrent fever, shortness of breath, rapid progression to acute dyspnea, and even life-threatening respiratory failure [8, 9]. The heterogeneous clinical presentation of PB and its potential to progress to severe but treatable respiratory failure highlights the need to raise awareness of this condition. The prevalence and clinical characteristics of PB in children have been largely understudied. This report aimed to explore the clinical characteristics, laboratory examinations,

imaging features and management of PB in children to ensure timely diagnosis and effective treatment. Furthermore, this study provide a comprehensive analysis of risk factors for multiple therapeutic FOB.

2. Subjects And Methods

2.1 Study population

269 children, initially diagnosed with pneumonia and confirmed as PB by bronchoscopy, were admitted to the Respiratory Department of Tianjin Children's Hospital from January 2015 to December 2019. This study was approved by the Ethics Committee of the Tianjin Children's Hospital. The patient data were collected and analyzed anonymously.

2.2 Diagnostic criteria

All patients presented with symptoms and signs suggestive of pneumonia on admission, including fever, cough, abnormal lung auscultation, and new infiltrations on chest radiography. Hypoxemia was defined as an oxygen saturation of < 92% recorded by pulse oximetry, measured under room air conditions[10]. MP infection was diagnosed if any of the two following diagnostic criteria were met. (a) An MP-immunoglobulin M (IgM) titer $\geq 1:160$; (b) 4-fold rise of the titer in acute and convalescent serum specimens; (c) Bronchoalveolar lavage fluid (BALF) MP-DNA $> 1.0 \times 10^6$ copies/L[11]. The indications for chest computed tomography (CT) included[12]: (a) An inconsistency between clinical manifestations and chest radiograph; (b) Suspected airway and lung malformations; (c) Serious complications associated with pneumonia; (d) Routine treatment was ineffective and after other diseases such as interstitial lung disease, and pulmonary tuberculosis, were excluded.

All cases underwent FOB and bronchoalveolar lavage (BAL) procedure based on the following criteria: (a) no improvement in clinical manifestations and chest radiography after one week of empirical treatment; in such circumstances, FOB and BAL were indicated to observe the presence of tracheomalacia, stenosis, foreign body obstruction, tuberculosis or alveolar hemorrhage and BAL fluid was collected for pathogenic analysis; (b) to relieve airway obstruction or pulmonary atelectasis caused by inflammatory secretions or necrotic substances which are often observed during refractory Mycoplasma pneumonia (RMPP), severe adenovirus pneumonia and influenza virus pneumonia; (c) diagnosis of airway injury after infection. Severe pneumonia of different etiologies can cause airway cartilage destruction, airway occlusion and other airway structural changes, which can be diagnosed and treated by FOB.

PB was diagnosed based on the following: (a) Bronchoscopy findings [13]: respiratory mucosa congestion, edema and increased mucus discharge; the bronchial lumen was blocked by inflammatory BCs, which were removed by biopsy forceps and appeared as "branch-like" structures after immersion in normal saline; (b) Histopathology findings: the inflammatory BCs consisted of inflammatory cells (predominantly eosinophils and neutrophils) and exfoliated epithelial cells, with positive immunohistochemistry staining for CD3, CD20, CD68, and MPO.

2.3 Inclusion criteria

Children aged less than 18 years old who met the diagnostic criteria of PB.

2.4 Exclusion criteria

(1) Patients with underlying diseases, such as congenital heart disease, asthma and congenital immunodeficiency disease. (2) Patients with a history of foreign body inhalation confirmed by FOB. (3) Patients with incomplete medical records.

2.5 Methods

Patient data, including the clinical characteristics, laboratory findings, imaging features, and drug management, were collected at admission.

Peripheral blood samples were also obtained on admission to determine the Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), interleukin (IL)-6, lactic acid (LA), lactic dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin (FER), D-dimer, fibrinogen (FG) and MP-specific antibody. Routine blood examinations were performed every 2–3 days and compared at admission and discharge. Chest computed tomography (CT) was performed before admission or during hospitalization in accordance with the criteria described above.

All the patients enrolled in our study underwent therapeutic FOB, and the BAL fluid was collected for microbiological determination according to the *Guide to pediatric bronchoscopy* [14]. Viruses were identified by direct immunofluorescence PCR, including adenovirus, respiratory syncytial virus, influenza virus, rhinovirus, human metapneumovirus. MP was detected using PCR or MP-IgM, and bacteria were detected by culture or multiplex PCR for respiratory bacteria pathogens.

2.3 Data analysis

Data were processed using SPSS 26.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median values (interquartile range) and assessed by independent group *t*-tests or Mann-Whitney *U* test. Categorical variables were expressed as percentage (%) and assessed by Chi-squared tests or Fisher's exact test. The paired *t*-test was applied to evaluate blood routine examination between admission and discharge. Receiver Operating Characteristic (ROC) curves and Logistic regression analyses were performed to identify variables related to multiple therapeutic FOB in PB patients. A two-sided *p*-value less than 0.05 was statistically significant.

3. Results

3.1 Detection rate of PB and its distribution in different seasons.

Among children (*n*=3840) diagnosed with pneumonia that underwent FOB and BAL from January 2015 to December 2019, PB was confirmed in 269 cases. The number of annual cases of PB increased from 2015

to 2019 (28, 29, 39, 65 and 108), while the number of annual cases of pneumonia treated with FOB and BAL was 516, 582, 658, 971 and 1113, respectively. The detection rate of PB in pneumonia was 5.4%, 5.0%, 5.9%, 6.7% and 9.7%, respectively from 2015 to 2019 (figure 1). The seasonal distribution of PB from 2015 to 2019 is shown in figure 2; the peak incidence was observed during the winter of 2019.

3.2 The etiology of PB.

In terms of the etiology of PB in the 269 children, no clear pathogen was detected in 12 cases, the positive detection rate was 95.5% (257/269), and mixed infections were detected in 30.9% (83/269). Among single-pathogen infections, MP was the predominant pathogen (61.0%, 164/269), followed by EB virus (1.5%, 4/269), influenza virus (0.7%, 2/269), *Candida albicans* (0.7%, 2/269), ADV (0.4%, 1/269) and *Streptococcus pneumoniae* (0.4%, 1/269). Out of the 83 cases of mixed infection, coinfection of MP and *Streptococcus pneumoniae* was the most common, with a prevalence rate of 8.6% (23/269), followed by MP and EB virus coinfection (6.3%, 17/269), MP and ADV (3.3%, 9/269), MP and influenza virus (3.3%, 9/269), MP and *Staphylococcus* (3.0%, 8/269), mixed infection (≥ 3 pathogens) (1.9%, 5/269), coinfection of different viruses (1.1%, 3/269), mixed viral and bacterial infection (1.1%, 3/269), MP and *Acinetobacter baumannii* (1.5%, 4/269), and MP and *Haemophilus influenzae* (0.7%, 2/269). (Table 1).

Table 1
The aetiological distribution in 269 children with PB

pathogens	patients (n)	infection rate(%)
MP	164	61.0
EB	4	1.5
Candida albicans	2	0.7
Influenzae	2	0.7
ADV	1	0.4
Streptococcus	1	0.4
no clear pathogens	12	4.5
MP + Staphylococcus	8	3.0
MP + Streptococcus	23	8.6
MP + Acinetobacter baumannii	4	1.5
MP + Haemophilus influenzae	2	0.7
MP + ADV	9	3.3
MP + Influenzae	9	3.3
MP + EBV	17	6.3
Mixed virus infection	3	1.1
Mixed virus and bacteria infection	3	1.1
Mixed infection (≥ 3 pathogens)	5	1.9

Table 2 Clinical characteristics of PB in children

Clinical characteristics	Patients (n=269)	Patients with single FOB (n=144)	Patients with multiple FOB (n=125)	P
Age, years	6.7±2.8	6.5±3.0	6.9±2.5	0.301
Sex(male/female)	137/132	70/74	67/58	0.414
Fever (n,%)	269 (100%)	144(100%)	125(100%)	1.000
Cough (n, %)	269(100%)	144(100%)	125(100%)	1.000
Peak body temperature, °C	40.0±0.6	39.9±0.6	40.2±0.6	0.001
Duration of fever, days	10.6±3.7	9.7±3.3	11.6±3.9	0.000
Duration of hospitalization, days	9.3±3.2	8.1±2.6	10.7±3.3	0.000
Hypoxemia (n,%)	62(23.0%)	24(16.7%)	38 (30.4%)	0.008
Pulmonary embolism (n,%)	3(1.1%)	0(0%)	3(2.4%)	0.062
Necrotizing pneumonia (n,%)	15(5.6%)	4(2.8%)	11(8.8%)	0.032
Complications of extrapulmonary (n,%)	144(53.5%)	58(40.3%)	68(54.4%)	0.021
Blood system (n,%)	16(5.9%)	9(6.3%)	7(5.6%)	0.822
Digestive system (n,%)	62(23%)	26(18.1%)	36(28.8%)	0.037
Cardiovascular system (n,%)	24(8.9%)	10(6.9%)	14(11.2%)	0.222
Rash (n,%)	40(14.9%)	22(15.3%)	18(14.4%)	0.840
Central nervous system (n,%)	21(7.8%)	6(5.6%)	10(10.4%)	0.140
Electrolyte disorder (n,%)	27(10%)	10(6.9%)	17(13.7%)	0.067
Data are presented as mean±SD, or <i>n</i> (%). Differences between groups were determined by independent group <i>t</i> tests(mean) and Chi-squared tests or Fisher exact test (proportions).				

Table 3 laboratory characteristics of PB in children

Laboratory information	Patients (n=269)	Patients with single FOB (n=144)	Patients with multiple FOB (n=125)	P
WBC($\times 10^9/L$)	8.6 $\pm$ 4.4	8.2 $\pm$ 4.4	9.1 $\pm$ 4.5	0.108
N%	71.2 $\pm$ 11.5	67.7 $\pm$ 11.7	75.2 $\pm$ 9.9	0.000
L%	21.1 $\pm$ 9.6	23.9 $\pm$ 10.1	17.9 $\pm$ 7.7	0.000
PLT($\times 10^9/L$)	263.4 $\pm$ 88.8	260 $\pm$ 98.2	265.9 $\pm$ 76.2	0.592
ESR, mm/h	30.0(21.0-42.3)	30.0(22.0-41.5)	29.0(21.0-44.0)	0.800
CRP, mg/L	39.4(19.0-76.0)	31.4(16.2-62.4)	58.3(29.8-86.2)	0.003
PCT, ng/ml	0.25(0.12-0.65)	0.20(0.10-0.49)	0.35(0.15-0.86)	0.001
IL-6, pg/ml	42.4(24.2-79.2)	38.1(20.6-71.1)	52.6(30.4-92.9)	0.010
LA, mol/l	2.67(2.11-3.29)	2.52(2.07-3.15)	2.76(2.25-3.43)	0.047
AST, U/L	39.0(30.0-58.0)	36.0(29.0-54.0)	43.0(31.0-61.0)	0.033
ALT, U/L	17.0(13.0-34.0)	15.0(12.0-26.0)	21.0(13.0-38.8)	0.018
LDH, U/L	532.0(396.0-706.0)	460.0(358.5-573.8)	625.0(460.0-809.0)	0.000
FER, ng/L	157.1(79.2-311.2)	106.0(63.9-193.3)	233.8(121.6-412.1)	0.000
FG, g/L	4.2(3.5-4.6)	4.2(3.5-4.6)	4.2(3.4-4.6)	0.896
D-dimer, mg/L	0.8(0.2-0.8)	0.5(0.3-1.3)	1.3(0.5-2.9)	0.000
Data are presented as mean $\pm$ SD and median (25th–75th percentile). Differences between groups were determined by the independent group <i>t</i> tests(mean $\pm$ SD) and Mann-Whitney <i>U</i> test (medians). WBC White blood cell, N Peripheral neutrophils, L Peripheral lymphocytes, PLT Platelets, ESR Erythrocyte sedimentation rate, CRP C-reactive protein, PCT Procalcitonin, IL-6 Interleukin (IL)-6, LA Lactic acid, AST Aspartate aminotransferase, ALT Alanine aminotransferase, LDH Lactic dehydrogenase, FER Ferritin, FG Fibrinogen.				

Table 4 Comparision of blood routine examination between at admission and at discharge

Laboratory information	Patients (n=269)	Patients with single FOB (n=144)	Patients with multiple FOB (n=125)
WBC($\times 10^9/L$)	8.6 $\pm$ 4.4	8.2 $\pm$ 4.4	9.1 $\pm$ 4.5
WBC ₂ ($\times 10^9/L$)	9.5 $\pm$ 3.1	9.2 $\pm$ 2.8	9.8 $\pm$ 3.3
P	0.000	0.001	0.008
N%	71.2 $\pm$ 11.5	67.7 $\pm$ 11.7	75.2 $\pm$ 9.9
N ₂ %	62.9 $\pm$ 12.5	62.5 $\pm$ 13.1	63.2 $\pm$ 11.9
P	0.000	0.002	0.000
L%	21.1 $\pm$ 9.6	23.9 $\pm$ 10.1	17.9 $\pm$ 7.7
L ₂ %	27.9 $\pm$ 11.1	28.2 $\pm$ 11.9	27.7 $\pm$ 10.2
P	0.000	0.003	0.000
PLT($\times 10^9/L$)	263.4 $\pm$ 88.8	260 $\pm$ 98.2	265.9 $\pm$ 76.2
PLT ₂ ($\times 10^9/L$)	410.7 $\pm$ 137.4	408.4 $\pm$ 140.9	411.5 $\pm$ 133.6
P	0.000	0.000	0.000
Data are presented as mean $\pm$ SD. Differences between at admission and at discharge were determined by Paired t test. WBC ₂ , N ₂ , L ₂ , PLT ₂ represented for the blood routine examination at discharge			

Table 5 Imaging characteristics of PB in children.

Imaging features	Patients (n=269)	Patients with single FOB (n=144)	Patients with multiple FOB (n=125)	P
Consolidation (n,%)	262(97.4%)	137(95.1%)	125(100%)	0.012
Atelectasis (n,%)	125(46.5%)	64(44.4%)	61(48.8%)	0.475
Pleural effusion (n,%)	127(47.9%)	56(38.9%)	71(56.8%)	0.003
Pleural thickening (n,%)	170(63.2%)	89(61.8%)	81(64.8%)	0.612
Data are presented as <i>n</i> (%). Differences between groups were determined by Chi-squared tests				

Table 6 Management of PB in children

Management	Patients (n=269)	Patients with single FOB (n=144)	Patients with multiple FOB (n=125)	P
Macrolides (n,%)	269(100%)	144(100%)	125(100%)	1.000
Combined application of antibiotics (n,%)	261(97%)	138(95.8%)	123(98.4%)	0.216
Glucocorticoid (n,%)	257(95.5%)	133(92.4%)	123(98.4%)	0.021
IVIG (n,%)	55(20.4%)	21(14.6%)	34(27.2%)	0.010
Admission to ICU (n,%)	48(17.8%)	22(15.3%)	26(20.8%)	0.238
Mechanical ventilation (n,%)	35(13.0%)	11(9.7 %)	24(16.8%)	0.085
Mortality (n, %)	3(1.1%)	2(1.4%)	1(0.8%)	0.646
Data are presented as <i>n</i> (%). Differences between groups were determined by Chi-squared tests				

Table 7 Multivariate logistic regression analysis for factors in patients with multiple FOB therapy

Variable	B	S.E.	Wald	P-value	OR	95%CI	
						Lower	Upper
N>75.5%	1.329	0.31	18.427	0.000	4.195	2.316	7.597
LDH>598.5U/L	1.004	0.335	8.974	0.001	3.640	1.957	6.771
DD>1.2mg/L	0.821	0.317	6.721	0.003	2.470	1.352	4.510

3.3 Clinical characteristics of PB in children.

The mean age of the patients was 6.7 ± 2.8 years (range, 9 months-14 years), and the male-to-female ratio was 1.04. The mean duration of fever and hospitalization was 10.6 ± 3.7 and 9.3 ± 3.2 days, respectively. All patients presented with cough and fever, and 62 (23.0%) cases suffered from hypoxemia. Of the 269 patients, 3 (1.1%) had a pulmonary embolism, 15 (5.6%) were diagnosed with necrotizing pneumonia, and 144 (53.5%) had extrapulmonary complications, including leukopenia (n=16, 5.9%), with digestive system abnormalities (nausea, vomiting, elevated transaminase, n=62, 23%), with cardiovascular system abnormalities (elevated myocardial enzymes, abnormal electrocardiogram, pericardial effusion and cardiac thrombosis) (n=24, 8.9%), rash (n=40, 14.9%), toxic encephalopathy (n=21, 7.8%), and electrolyte disorders (n=27, 10%).

Among the 269 patients, 144 cases underwent FOB and BAL once (single treatment group), and 125 underwent multiple times (multiple treatment group). There was no statistical difference between the two groups in age, sex ratio and incidence of fever. Compared with the single treatment group, children in the multiple treatment group exhibited higher peak body temperature, longer duration of fever and hospitalization. The total incidence of extrapulmonary complications was higher in the multiple treatment group, especially for the digestive system. (Table 2)

3.4 Laboratory characteristics of PB in children.

Laboratory indicators of PB cases in our study are summarized in Table 3. Higher levels of ESR (30mm/h), CRP (39.4 mg/L), PCT (0.25ng/ml), IL-6 (42.4pg/ml), LA (2.67mmol/L), LDH (532U/L), FER (157.1ng/L) and D-dimer (0.8mg/L) were observed in PB patients. The levels of N% (75.2 vs. 67.7%), CRP (58.3 vs. 31.4 mg/L), IL-6 (52.6 vs. 38.1 pg/ml), LA (2.76 vs. 2.52 pg/ml), ALT (21.0 vs. 15.0 U/L), AST (43.0 vs. 36.0U/L), LDH (625.0 vs. 460.0U/L), FER (233.8.0 vs. 106.0ng/L), D-dimer (1.3 vs. 0.5mg/L) in the multiple treatment group were significantly higher than in the single group ($P_s < 0.05$). (Table 3)

3.5 Comparision of blood routine examination between admission and discharge

We further compared the changes in blood routine tests at discharge and admission. Results indicated that compared with admission results, patients at discharge tended to have higher levels of white blood cell (WBC) (9.5 vs. $8.6 \times 10^9/L$, $P < 0.05$), L% (27.9% vs. 21.1%, $P < 0.05$), platelet count (410.7 vs. $263.4 \times 10^9/L$, $P < 0.05$) and decreased levels of N% (71.2% vs. 62.9%, $P < 0.05$) (Table 4).

3.6 Imaging characteristics of PB in children.

All the 269 enrolled patients underwent chest CT scan imaging, with 262 (97.4%) cases of pulmonary consolidation, 125 (46.5%) of segmental or lobar atelectasis, 127 (47.9%) of pleural effusion and 170 (63.2%) of pleural thickening. The incidence of pulmonary consolidation and pleural effusion was higher in the multiple treatment group (100% vs. 95.1%, 56.8% vs. 38.9%, respectively, $P < 0.05$). (Table 5)

3.7 Management of PB in children

All patients received at least one type of antibiotic before admission. The 269 subjects were prescribed anti-MP antibiotics empirically, consisting of macrolides (n=197, 73.3%), doxycycline (n=52, 19.3%), and quinolones (n=20, 7.4%). The combination of antibiotics (including anti-MP) with anti-bacteria or anti-influenza virus was prescribed in 261 (97%) cases. 257 (95.5%) cases received oral or intravenous glucocorticoid, 55 (20.4%) received intravenous immunoglobulin (IVIG), 48 (17.8%) were admitted to the intensive care unit (ICU), and 35 (13%) received mechanical ventilation. The multiple treatment group exhibited a higher proportion of glucocorticoid and IVIG therapy than the single treatment group (98.4% vs. 92.4%, 27.2% vs. 14.6%, respectively, $P < 0.05$). FOB and BAL were used to remove mucus plug and BCs. Three children died of acute respiratory distress syndrome (ARDS) and multiple organ failure due to failure to remove the casts in time. (Table 6)

3.8 Risk factors for patients with multiple FOB therapy

Univariate analysis showed that the peak body temperature, duration of fever and hospitalization, hypoxemia, extrapulmonary complications, presence of pleural effusion, higher level of inflammation indicators and D-dimer were significant factors associated with multiple FOBs. ROC analysis revealed that N%, LDH and D-dimer had significant prognostic values in identifying subjects that required multiple FOB, with optimal cutoff values of 75.5%, 598.5U/L and 1.2mg/L, respectively. To adjust for the influence of confounders, multivariate logistic regression analysis was performed, and results showed that N%, LDH and D-dimer were independent risk factors for multiple FOBs with odds ratio (OR) values of 4.19, 3.64 and 2.47, respectively. (Table 7)

4. Discussion

It has long been thought that the majority of pediatric cases of PB were associated with surgical correction of congenital heart disease. In the past ten years, an increasing number of studies have reported that PB in children is related to respiratory infections [3–7]. However, most studies on PB and BCs consist of case reports or small case series, with few comprehensive reports of PB published in the literature. In this regard, Lu S et al. [6] reported 22 cases of BCs among 161 children with *M. pneumoniae* pneumonia (MPP) that underwent therapeutic FOB and BAL from November 2015 to December 2016. Moreover, PB in 63 children associated with the influenza virus was analyzed in a study by Wei F et al. [15]. The incidence of PB remains largely unclear. However, it should be borne in mind that PB may be underdiagnosed due to its rarity, limited pediatrician awareness, and milder presentation in some children. In the present study, we identified 269 children with PB from 3840 cases of pneumonia that underwent therapeutic FOB and BAL between January 2015 and December 2019. We estimated that PB accounted for 7.0% of children with pneumonia requiring FOB. The 269 cases of PB were related to respiratory tract infections. We reviewed the etiology, clinical manifestations, treatment and further explored the risk factors of multiple therapeutic FOB in children with PB.

We found that MP, bacteria, influenza virus, ADV and *Candida albicans* could trigger PB. In recent years, the association between PB and MP has been reported in various studies. In a study that enrolled 15 children with PB, MP infection accounted for 86.7% of the cases [4]. Moreover, in a study by Guo et al., MP

infection was detected in 90.4% of children with type I PB (n=73) [16]. In the present study, MP was identified in the majority of patients (n=241, 89.6%), including single MP infection in 164 (61.0%) cases and mixed infections of MP with bacteria and/ or virus in the remaining (n=77, 28.6%) subjects. Moreover, the seasonal distribution of PB from 2015 to 2019 indicated that the peak incidence of PB was in winter. Yan X et al. also demonstrated that MPP had a higher prevalence rate in winter in a 3-year retrospective analysis [17]. The significant detection rate of MP in PB cases and epidemic consistency between PB and MPP indicated that MP is a prominent pathogen associated with PB.

Whether the cause of PB is actually related to respiratory infections remains largely unknown. The possible mechanisms may be attributed to pathogens that directly damage the airway and are secondary to the inflammatory process. MPP is usually considered self-limited and benign(18); however, it may progress to severe or fulminant pneumonia and become life-threatening [18, 19]. Previous studies [6, 20, 21] also showed that MP infection could lead to varying degrees of respiratory mucus plugs, even BCs, resulting in PB. The mechanism underlying the role of MP infection in PB could be that MP infection directly causes damage to the airway, including epithelial necrosis to block the respiratory tract and cilia shedding to cause cilia removal dysfunction and promotes airway hypersecretion induced by excessive inflammation[22, 23]. Compared with bacterial and viral infections, MP infection has a greater tendency to induce an excessive inflammatory response in the body[24], thus inducing the continuous formation of mucus plug in the airway and causing damage to the whole body.

In the present study, the mean age of patients was 6.7 ± 2.8 years (range, 9 months-14 years), similar to the results reported in a previous study (6.1 ± 2.8 years) [16]. School-aged children have a mature immune system and are prone to develop strong immune responses, leading to airway mucosal damage that increases the tendency to form BCs that block the airways. There are currently no definitive diagnostic criteria or tests for PB. The diagnosis of PB is mainly clinical and is based on the clinical presentation (expectoration of casts), bronchoscopic, and imaging findings. The clinical manifestations of PB are diverse, including fever, cough, dyspnea or respiratory distress and extrapulmonary damage. Rapid progression to hypoxemia can be regarded as a strong indicator of PB. However, when patients with mild symptoms have no or mild signs of hypoxemia, it can be difficult for clinicians to recognize it. In our study, 62 (23.0%) cases suffered from hypoxemia. Li W et al. (18)revealed that all children (n=15) in their study with PB showed no signs of hypoxemia, while Lu S et al. [6] reported that only 9 out of 22 children with MPP BCs required oxygen therapy. All the above findings suggest that hypoxemia is not a sensitive indicator to identify PB. The poor specificity of signs and symptoms emphasizes the importance of obtaining a detailed history and physical examination along with chest imaging and bronchoscopic evaluation.

ICU treatment in our study was required in 17.8% of cases (48/269), which was lower than reported by Lu et al. (58.3%, 14/24 cases) [25]. Moreover, three children died of acute respiratory distress syndrome (ARDS) and multiple organ failure due to failure to remove the casts in time. The incidence of critically ill patients and mortality was significantly lower than in the literature[8, 26]. Indeed, the clinical manifestations of PB depend on the location and degree of bronchial obstruction, ranging from

fragmented, partial BCs to a large and complete cast that fills the entire airway[6]. However, it should be borne in mind that rapid therapeutic FOB is highly effective and can prevent the development of respiratory failure.

We found that patients in the multiple FOB group exhibited severe clinical manifestations, including higher peak body temperature, longer duration of fever and hospitalization, higher incidence of intra and extrapulmonary complications, and higher levels of inflammation indicators and D-dimer. Furthermore, multiple logistic regression found that $N\% > 75.5\%$, $LDH > 598.5U/L$, and $D\text{-dimer} > 1.2mg/l$ were independent risk factors for multiple therapeutic FOB. Previous studies have found that a high neutrophil count was positively correlated with excessive inflammation and disease severity in children with MPP [27], which was attributed to the fact that increased neutrophils can injure the airways during the acute stage through the release of proteases, reactive oxygen and inflammatory cytokines[28]. LDH is a nonspecific inflammatory biomarker present in the cytoplasm. Xu et al.[29] identified LDH as an independent risk factor for mucus plug formation in children with RMPP. In our study, $LDH > 598.5U/L$ was a predictor for multiple therapeutic FOB. Although the pathogenesis of PB is still widely unknown, it is commonly believed that PB triggered by infection results from an inappropriate immune response to infection and direct damage of pathogen to the airway[3, 30]. The higher levels of inflammation biomarkers indicated excessive inflammation, leading to continuous formation of mucus plugs, requiring multiple therapeutic FOBs to clear the BCs.

It is widely acknowledged that an increase in D-dimer is an important indicator of high fibrinolysis, representing blood hypercoagulability and the presence of thrombi [31]. Recently, D-dimer has also been recognized as an indicator for evaluating the severity of MPP. Jin X et al. reported higher D-dimer levels in children with severe MPP than in children with mild disease (0.61 vs. $0.30mg/L$) [32]. In Yan Z et al.'s research[33], the D-dimer level was positively correlated with inflammatory markers ($N\%$, CRP, LDH, IL-10), suggesting that higher levels of D-dimer were associated with severe inflammation. In the present study, we found an elevated D-dimer level in PB children, and $D\text{-dimer} > 1.2mg/l$ was a risk factor for multiple therapeutic FOB and BAL, consistent with the study by Zhang et al.[34]. This study showed that children receiving multiple therapeutic FOB for RMPP had higher D-dimer levels (1.808 mg/L) than the monotherapy group ($0.567mg/L$). In summary, we speculate that a high D-dimer level is an indicator of excessive inflammation, which plays an important role in inducing mucus plugs formation in PB and is an important risk factor for patients requiring multiple therapeutic FOB.

The imaging features of PB in children are heterogeneous, including pulmonary consolidation, atelectasis, pleural effusion, emphysema and pneumothorax[16, 35]. A recent study [18] found that 13 out of 15 PB children presented with lung consolidations involving unilateral or bilateral infiltrations, and 5 cases developed pleural effusion. Our results showed the poor specificity of imaging findings associated with PB and a high incidence of lung consolidation (97.4%), consistent with previous reports (98.6%)[16]. Overall, the presence of persistent atelectasis in chest imaging is a strong indication for therapeutic FOB. The incidence of atelectasis in our research was 46.5% . In a study by Lu S et al.[6], 6 out of 22 children with BCs and lobar consolidation also presented with atelectasis. Timely therapeutic FOB is often not

possible when PB patients have no signs of atelectasis. Compared with atelectasis, PB should be considered when patients with persistent fever and large chest imaging infiltration

Although PB presents with severe clinical manifestations and the critical form in children has a mortality rate as high as 7-10% due to failure to extract BCs in time[8, 9, 26], the prognosis of PB is generally favorable if the disease can be treated promptly. The lack of in-depth knowledge of the underlying pathophysiology has not prevented the gradual evolution of effective treatment options for symptomatic relief and correction of underlying causes of PB. Most reports of effective therapy are based on standard antibiotic treatment, glucocorticoids, IVIG and clearance of BCs with FOB[4, 6]. In agreement with this notion, all patients in the present study received appropriate antibiotic treatment; up to 95.5% of subjects received glucocorticoid therapy, and 20.4% received IVIG to modulate immunity. Glucocorticosteroid and IVIG have been confirmed to be effective in reducing inflammatory cast formation and alleviating PB symptoms. It is worth noting that the essence of BCs is the accumulation of thick mucus plugs. A majority of the PB patients present with a high fever. Indeed, the loss of water from the respiratory tract cannot be underestimated, resulting in the thickening of the mucus secretions. Accordingly, ensuring an adequate fluid intake is essential. During the early stage of the disease, techniques that improve expectoration, including moisturizing the airway, mechanical vibration expectoration, local application of phlegm-reducing drugs and glucocorticoids, can prevent the formation and improve the discharge of BCs. It has been established that FOB is highly efficient for the treatment of PB, including clearance of BCs to improve lung ventilation and various inflammatory factors and easy access to the lower airway for pathogenic detection. Recent studies [36, 37] found that compared with late therapeutic FOB, FOB therapy during the early disease process in RMPP patients with large pulmonary lesions resulted in faster recovery of clinical and inflammation biomarkers and shorter hospital stay. Furthermore, a considerable number of children with PB require multiple therapeutic FOBs. In our study, the proportion of patients in the multiple FOB group was 46.5% (125/269), consistent with the results of Cai L et al.[38], who showed that more than 50% of children with PB required multiple therapeutic FOB and all patient had favorable outcomes.

There were several limitations to this study. First of all, the retrospective nature of our study suggests that our findings may be subject to selection bias. Moreover, the patients were enrolled from a single center, and the results cannot be extrapolated to patients from other regions. Indeed, to enhance the robustness of our findings, an RCT study should be designed.

5. Conclusion

In conclusion, our study showed that MP is a significant pathogen associated with PB. The clinical manifestations of PB are not specific. Children with PB experience persistent fevers, excessive inflammation and severe radiological findings. FOB is an effective treatment for patients with PB, and in some cases, multiple therapeutic FOBs are required for cast removal. N% >75.5%, LDH >598.5U/L and D-dimer >1.2mg/L are important risk factors for multiple FOB procedures. A favorable prognosis can be expected with timely diagnosis and therapeutic FOB, when appropriate.

Abbreviations

PB (plastic bronchitis), FOB (fiberoptic bronchoscopy), MP (Mycoplasma pneumoniae), BCs (bronchial casts), ADV (adenovirus), BAL (bronchoalveolar lavage), PCR (polymerase chain reaction), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), PCT (procalcitonin), IL-6 (interleukin), LA (lactic acid), LDH(lactic dehydrogenase), ALT (alanine aminotransferase), AST (aspartate aminotransferase), FER (ferritin), FG (fibrinogen) CT (Chest computed tomography), IVIG (intravenous immunoglobulin), ICU (intensive care unit), MPP (Mycoplasma pneumoniae pneumonia), RMPP (refractory Mycoplasma pneumoniae pneumonia), ROC (Receiver Operating Characteristic).

Declarations

Acknowledgments

The authors wish to thank the patients and participating investigators and staff associated with the clinical studies discussed here.

Funding.

This work was supported by the National Natural Science Foundation of China [Grant number 81771589], the Key Project of Tianjin Health Care Professionals [Grant number16KG166] and the Program of Tianjin Science and Technology talent cultivation [Grant number RC20020].

Availability of data and materials

The data used in this report are available from the corresponding author on reasonable request.

Author contributions.

All authors contributed to the intellectual content of this manuscript and approved the final manuscript as submitted. (I) Conception and design: Jianghua Zhan and Xiaojian Cui; (II) Administrative support: Yongsheng Xu; (III) Provision of study patients: Linsheng Zhao and Wei Guo; (IV) Collection, assembly of data: Tongqiang Zhang and Lihua Zhao; (V) Data analysis and interpretation: Wei Guo and Linsheng Zhao; Search of the literature: Jiafeng Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Tianjin Children's Hospital (No. L2020-02), and individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interest.

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Figures

Figure 1

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Figure 2 Seasonal distribution of patients from 2015 to 2019

Figure 2

"See image above for figure legend"

Figure 3. (A and B) Chest CT demonstrates consolidation and atelectasis in the inferior lobe of the left lung before bronchoscopy. (C and D) Bronchoscopy showed that the bronchial opening was blocked by dense mucus casts. (E and F) Bronchial plastic findings were removed from the patients via bronchoscope.

Figure 3

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