Longitudinal Assessment of Pulmonary Function and Bronchodilator Responses in Pediatric Patients with Post-Infectious Bronchiolitis Obliterans

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Abstract

Abstract Objective: We aimed to further assess the evolution of pulmonary function and bronchodilator response in the Chinese case series with post-infectious bronchiolitis obliterans (PIBO). Methods: Twelve children with PIBO, aged 59-110 months, were retrospectively studied between 2011 and 2019. According to the ATS/ERS recommendations, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC and maximal midexpiratory flow velocity 25%-75% (MMEF25%-75%) were collected at each pulmonary function tests (PFTs), as well as bronchodilator responses were evaluated. Spirometric parameters were monitored over time, and generalized linear mixed models were used to analyze longitudinal panel data. Results: The median baseline PFT values for FVC, FEV1, FEV1/FVC ratio and MMEF25% -75% were 41.6%, 39.75%, 90.7% and 22.2% respectively. At the initial PFTs, 10 (83.3%) patients demonstrated a significant bronchodilator response. FVC and FEV1 increased by a mean of 8.212%/year and 5.007%/year, and FEV1/FVC ratio with an average decrease of 3.537%/year. MMEF25-75% showed an average increase of 1.583% per year. Over all, FEV1 and MMEF25%-75% showed different degrees of improvement after inhaled bronchodilators at each PFT sessions for ten patients, and FEV1 was with significant (>12%) β2-bronchodilation in 53% of PFT sessions. Conclusions: Pediatric patients with PIBO showed an obstructive defect of pulmonary function. The FVC, FEV1 and MMEF25%-75% improved as they grew old, while FEV1/FVC ratio decreased. It may be due to the development of lung parenchyma more than airway growth. Airway obstruction of some patients improved with the use of β2 agonists.

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Abbreviations

PIBO

post-infectious bronchiolitis obliterans

PFTs

pulmonary function tests

FVC

forced vital capacity

FEV_1

forced expiratory volume in one second

$MMEF_{25\%-75\%}$

maximal midexpiratory flow velocity25%-75%

HRCT

high resolution chest computed tomography

Abstract

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Methods: Twelve children with PIBO, aged 59-110 months, were retrospectively studied between 2011 and 2019. According to the ATS/ERS recommendations, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC and maximal midexpiratory flow velocity 25%-75% ($MMEF_{25\%-75\%}$)were collected at each pulmonary function tests (PFTs), as well as bronchodilator responses were evaluated. Spirometric parameters were monitored over time, and generalized linear mixed models were used to analyze longitudinal panel data.

Results: The median baseline PFT values for FVC, FEV_1, FEV_1/FVC ratio and $MMEF_{25\%-75\%}$ were 41.6%, 39.75%, 90.7% and 22.2% respectively. At the initial PFTs, 10 (83.3%) patients demonstrated a significant bronchodilator response. FVC and FEV_1 increased by a mean of 8.212%/year and 5.007%/year, and FEV_1/FVC ratio with an average decrease of 3.537%/year. $MMEF_{25-75\%}$ showed an average increase of 1.583% per year. Over all, FEV_1 and $MMEF_{25\%-75\%}$ showed different degrees of improvement after inhaled bronchodilators at each PFT sessions for ten patients, and FEV_1 was with significant (>12%) β_2-bronchodilation in 53% of PFT sessions.

Conclusions: Pediatric patients with PIBO showed an obstructive defect of pulmonary function. The FVC, FEV_1 and $MMEF_{25\%-75\%}$ improved as they grew old, while FEV_1/FVC ratio decreased. It may be due to the development of lung parenchyma more than airway growth. Airway obstruction of some patients improved with the use of $\beta_2$agonists.

Short title: Longitudinal Assessment of Pulmonary Function of PIBO children

Keywords: post-infectious bronchiolitis obliterans, children, pulmonary function, bronchodilator responses, longitudinal assessment

Introduction

Bronchiolitis obliterans (BO) is a rare small airway injury-related chronic inflammation airflow obstruction syndrome. Many conditions may trigger BO, such as infection, lung transplantation, bone marrow transplantation, toxic gases, chronic aspiration, connective tissue diseases, and certain drugs[1]. In which, post infectious BO (PIBO) is especially common in children. There are reports of PIBO secondary to infection with adenovirus, influenza, parainfluenza, respiratory syncytial virus, measles virus, and mycoplasma pneumonia and so on[2-4]. Histopathological features of PIBO include the concentric narrowing and obliteration of small airways due to an inflammatory process surrounding the bronchiolar lumen[5]. Its primary clinical manifestations are usually repeated cough, wheezing and shortness of breath, accompanied by varying degrees of dyspnea and decreased activity tolerance. In addition to clinical characteristics, pulmonary function shows a severe airway obstruction, and high resolution computed tomography (HRCT) shows characteristic mosaic patterns and bronchiectasis[2,3]. Some scholars have suggested a PIBO score to diagnose the disease.

In which, the typical clinical history represents four points, adenovirus infection three points, and chest HRCT with mosaic perfusion pattern four points. A score above 7 predicted the diagnosis[6].

In PIBO, as in other chronic lung diseases, determining pulmonary function is important for the diagnosis, classifying the severity of the condition and monitoring its progression. PIBO usually occurs in infants[4], which cannot perform the spirometry maneuver, and some patients were lost during the follow-up periods, so there has been only a few study that followed its evolution on the basis of the pulmonary function tests (PFTs)[7-10]. On the other hand, PIBO is a rare disease, although it was first described in 1901 by German pathologist Lange, we does not recognize and diagnose the disease for a long time. Our current knowledge about the evolution of pulmonary function in children with PIBO is limited and controversial. It usually considered PIBO as a disorder involving fixed obstruction with no significant bronchodilator response. Some authors observed pulmonary function in PIBO patients was unchanged even declined with growth[8,9]. However, other previous study demonstrated lung function slowly improved[7,10], and it was reported that some patients with PIBO showed positive β_2 agonist responses[8,11,12].The objective of this study was to further assess the evolution of pulmonary function and bronchodilator response in the Chinese case series with PIBO. Profiling the longitudinal pulmonary function of children with PIBO could be beneficial to study and treat the disease.

Methods

This study involved a retrospective analysis of the clinical data, PFT results and radiographic features of patients diagnosed with PIBO between 2011 and 2019 at the First Hospital of Jilin University. The study was approved by the research ethics committees of our institutions. All tests were ordered as part of clinical care of patients with PIBO. All participating patients and the parents or legal guardians verbally consented to be included in the study.

Participants

Twelve children were included during the study period, and data were obtained from clinical records. The average age at diagnosis was 36 months. All patients were diagnosed with PIBO according to a history of severe lower respiratory infection or acute lung injury in previously healthy subjects; exercise intolerance, recurrent or persistent wheezing, coughing and tachypnea with extensive wheezing and moist crackles in lungs lasting for more than 6 weeks; severe obstructive lung disease on PFTs; characteristic changes of mosaic perfusion pattern, bronchial wall thickening, bronchial dilation and vascular attenuation on chest HRCT[6]; bronchopulmonary dysplasia, cystic fibrosis (CF), pulmonary tuberculosis, immunodeficiency and congenital heart disease were excluded on the basis of clinical, radiological and laboratory data. We followed their PFT results since they were able to perform the spirometry maneuver until November 2019. The average time was 29 months (range of 6-80months) for follow-up of PFTs.

PFT

Spirometry were performed in the pulmonary function laboratory through Jaeger Master Screen Paed (Jaeger Company, Wurzburg, Germany) by a trained physician and following American Thoracic Society (ATS)/European Respiratory Society (ERS) performance criteria for acceptability and reproducibility[13].

Actual flows (FEV_1 in L; maximum mid-expiratory flow 25%-75%, $MMEF_{25\%-75\%}$ in L/s) and lung volumes(FVC, in L)were normalized according to ethnicity, sex, height and reference equations. The initial data of PFTs in each patient were obtained when they were able to perform the maneuver, median age of 78 months (range: 59-110 months). And PFTs were followed for an average of about 29 months (range: 6-80 months). PFTs were performed when patients had been clinically stable for at least two weeks, at the same place, the same device and by the same physician. Mouth seal around the mouthpiece, breathing patterns even the body position were careful assessed. Prior to the PFTs, long- and short-actingβ_2 agonists were with held for 48 and 12h, respectively. According to the ATS/ERS recommendations, the severity of obstructive functional impairment was defined based on the FEV_1. The main methods for assessing bronchodilator responses are described in Chart 1. Besides we also analyzed factors that might have influenced

the bronchodilator response at the initial PFTs.

Chart 1. Description of different methods (equations) for calculating a bronchodilator response.

Percent variation from the previous (pre-bronchodilator) measurement:

(FEV_1 post - FEV_1pre)/(FEV_1 pre × 100)

Absolute volume change from the previous (pre-bronchodilator) measurement: FEV_1post - FEV_1pre Post: post-bronchodilator; and pre: pre-bronchodilator. $MMEF_{25\%-75\%}$ was alike.

Statistical analysis

Longitudinal data analysis was used to assess the change in PFTs over time. Quantitative data is expressed as median and interquartile range, whereas qualitative data is described by frequency (composition ratio). Generalized linear mixed models were assessed with age at PFTs as the fixed effects, while random effects were specified at the level of the individual. All decreases and increases in PFT parameters were described as changes in percentage of predicted for height. At the initial PFTs, we used a linear mixed model to determine whether bronchodilator responses were affected by patient age at the time of diagnosis, or by allergy factors (including a history of wheezing, atopic dermatitis and family asthma history). All data were analyzed using R software (v3.5.3, Auckland, New Zealand). The p value<0.05 was considered to be statistically significant.

Result

Clinical characteristics

All patients were healthy previously, and the average age at the diagnosis was 36 months. The sex distribution was eight males (67%) and four females (33%). The racial/ethnic was Han. During the initial acute lower respiratory tract infection, adenovirus antigen was positive in four individuals by testing nasopharyngeal secretions, mycoplasma pneumoniae was identified in four patients and measles virus in one patient by serum IgM antibody tests, and the etiology was unknown in two patients. In addition, one patient was infected with both adenovirus and mycoplasma pneumoniae (Table 1). The diagnosis of PIBO was made on the basis of the clinical and radiographic findings. The patients presented with wheezing, cough, dyspnea, exercise intolerance, and frequent respiratory illness. Physical examination findings were persistent moist crackles, extensive wheezing and hypoxemia. In all twelve patients, HRCT scans demonstrated mosaic perfusion pattern, air trapping and bronchial wall thickening. In one patient, bronchial dilation was showed (Figure 1A and B).

PFT results

Baseline PFTs

Initial PFTs were accomplished at the age that each patient could perform the maneuver (median:78 months; range: 59-110) according to the guidelines established by the ATS/ERS. The median duration of the PIBO disease at the time of initial PFTs was 43 months. All PFT data of patients showed consistent with moderate to severe obstruction. At baseline, the median PFT values (based on percentage of predicted value for a given age) for FEV_1, FVC, FEV_1/FVC ratio and $MMEF_{25\%\ -75\%}$ were 39.75%, 41.6%, 90.7% and 22.2% respectively (Table 2).

Post-bronchodilator improvements were significant in expiratory flows, although the values didn't reach normality for age. Of the 12 pediatric PIBO patients, 10 (83.3%) demonstrated a significant bronchodilator response when the cut-off point was a percent change of 12%, as recommended by the ATS/ERS (data was not given). As showed in Table 3, FEV_1 was significantly improved after inhalation of bronchodilators, and MMEF25%-75% alike. The mean percent variation and the mean absolute volume change from the previous measurement were 23.01% and 0.15 L for FEV_1, 46.92% and 0.28L/s for $MMEF_{25\%-75\%}$ respectively. In the multivariate analysis of the outcome variables, we found that the predictor variables (age at diagnosis, allergy factors) had no significant effect on the bronchodilator response, although the higher diagnosis age will reduce the improvement value of $MMEF_{25\%-75\%}$($P<0.05$) (Table 4).

Final PFTs

The median duration of follow-up was 29 months (range: 6-80 months). At the final PFTs, the median values for FEV_1, FVC, FEV_1/FVC ratio and $MMEF_{25\%–75\%}$ were 57.8%, 76.1%, 77.85% and 26.2% respectively (Table 2), while the children with positive results for bronchodilator responses were 7 (58.3%) (data was not given). The improvements were also significant when the mean percent variation from the previous measurement was calculated (increases of 15.89% and 24.65% for $FEV_1$and $MMEF_{25\text{-}75\%}$, respectively). The improved percentage was not as high as that in the baseline PFTs. And the mean absolute volume change was 0.16 L for FEV_1 and 0.18L/s for $MMEF_{25\%\text{-}75\%}$ (Table 3).

Progression of PFTs

The total number of PFTs was different for each patient (median 6; range:2-17). At each PFTs, FVC, FEV_1, FEV_1/FVC and $MMEF_{25\%\text{-}75\%}$ were all performed in all patients. The median time interval between each PFTs was 9 months (range: 1-35 months). There was significant inter- and intra-individual variability in every PFT parameter over time (Figure 2). However, even after taking that into account, over time, the FVC and FEV_1 improved in eleven children and was only mild decrease in one child, FVC and FEV_1 increased by a mean of 8.212%/year (95% CI: 6.531%-9.894%; $p<0.0001$) and 5.007%/year (95% CI: 3.463%-6.552%; $p<0.0001$) (Table 2, Figure 2). But the increase in FEV_1 was not as significant as FVC, so there was a unanimous and significant fall in FEV_1/FVC ratio with an average decrease of 3.537%/year (95% CI: 1.984%-5.09%; $p<0.0001$) (Table 2, Figure 2). $MMEF_{25\%\text{-}75\%}$ improved in nine children and unchanged or declined slightly in three children, resulting in an average increase of 1.583% per year (95% CI: 0.046%-3.12%; $p<0.05$) (Table 2, Figure 2).

Over all, FEV_1 and $MMEF_{25\%\text{-}75\%}$ showed different degrees of improvement after inhaled bronchodilators at each PFT sessions for ten patients, and FEV_1 was with significant (>12%) β_2-bronchodilation in 53% of PFT sessions. (Figure 2, data was not given).

Discussion

This investigation followed the PFT changes over time in pediatric patients with PIBO, diagnosed on the basis of previously mentioned characteristic clinical and HRCT findings with a PIBO score>7. In our study, patients always showed impaired pulmonary function with an obstructive pattern, but improvement in pulmonary function were observed. We found that our sample of twelve children diagnosed with PIBO, on average, has an FVC and FEV_1 that has much increased; however, FEV_1/FVC declined significantly over time.

Most of our studied subjects developed PIBO before 3 years of age (66.7%), there were also two children at pre-school and two at school age diagnosed with PIBO in the study, and they were all Han race. Adenovirus and mycoplasma were the predominant microorganism involved in the PIBO pathology, occurring in 75% of the patients together (nine out of twelve patients), which is similar to the results reported in previous studies[3,14,15]. In addition, measles virus was also a common cause. We also found that six individuals required mechanical ventilation, which may be an independent risk factor for developing PIBO[16].

In this group of patients, typical findings on HRCT chest scan were defined as a mosaic perfusion pattern, because of patchy areas of hyperinflation and vascular attenuation, whereas air trapping was more apparent in expiration. We also identified bronchial wall thickening and bronchial dilation. These HRCT findings were consistent with previous studies in patients with PIBO[2,3].

PFTs are important ancillary studies, whether for diagnosis or follow-up of patients with PIBO. There were pronounced decrease in FEV_1, FEV_1/FVC and $MMEF_{25\%\text{-}75\%}$ in the study, which are characteristic of obstructive airway disease, especially small airway. Our findings corroborate the conclusion that pediatric patients with PIBO have a common pattern of severe pulmonary function impairment, characterized by marked airway obstruction[17-19]. Meanwhile, the decrease of FVC seemed to be combined with restrictive dysfunction, but it does not really restrict when lung volumes measured by plethysmography are available.

In our patients, we observed that FVC, FEV_1, and $MMEF_{25\text{-}75\%}$ were much improved over time. FVC increased more than FEV_1, so the FEV_1/ FVC significantly decreased. Although spirometry parameters increased, pulmonary function remained moderately impaired in childhood, especially small airways. The pulmonary function improved indicates that airway damaged with conserved normal lung growth. That is, the concept of the neoalveolisation throughout childhood and adolescence postulated by Narayanan et al[20]. The fact that FEV_1/ FVC ratio decreased is probably because of the unequal growth of the lung parenchyma and airways, indicative of a 'dysynaptic growth' of the lung. However, this catch-up growth after the lung injury could be possible in terms of alveolar number, but may be not as much for airway size[20,21]. Such as those with PIBO, are more likely to be volume responders than flow responders[22]. This has been demonstrated by some other studies [7,10] and confirmed by the present case series. Some else research draw different conclusions just like longitudinal data from 6 children showed unchanged abnormal lung function many years after treatment[8], and a study including 11 patients with PIBO, reported that pulmonary function declined with growth[9]. It is possibly because we included a homogeneous group of younger children who have more opportunities for alveolar development, and relatively not severe forms of the symptom.

At the initial PFTs, 10 (83.3%) pediatric PIBO patients demonstrated a significant bronchodilator response according to the ATS/ERS recommendations, that is, FEV_1 was significantly improved after inhalation of bronchodilators (on average 23.01%), but the children with positive results decreased during the follow-up, it was 7 (58.3%) at the final PFTs. And longitudinal assessment of the bronchodilator response over the follow-up period demonstrated that positive response for FEV_1 remained in over half PFT sessions (Figure 2). In children with PIBO, the most severe obstruction is at the small airway, so we observed the higher $\beta_2$agonist responses in terms of the $MMEF_{25\%\text{-}75\%}$. However, $MMEF_{25\%\text{-}75\%}$ is usually highly variable in control groups and lacks the consistent standard, therefore the variation is not easily interpreted[23]. Although, theoretically, a bronchodilator response should be absent in children with fixed airway obstruction such as in PIBO, there is controversy regarding reversibility of airway obstruction in PIBO. Mattiello R et al. reported 72 children with PIBO that the bronchodilator response was significant in 42 patients (58.3%),and they considered that age at viral aggression, a family history of asthma, and allergy had no significant effects on bronchodilator responses[10]. HL Chung et al. observed bronchial hyper responsiveness was in more than 40% of PIBO patients and it was not related with the atopic status of the patients[24]. We also found that neither age at diagnosis, nor allergy factors had any significant effect on the magnitude of the bronchodilator response. And some patients with PIBO show hyperresponsiveness to methacholine[25]. Castro-Rodriguez et al. using impulse oscillometry also observed a significant bronchodilator response in children with PIBO in Chile[14].

The concept of PIBO as irreversible, fixed obstruction does not seem to apply to all pediatric patients with PIBO. The mechanisms underlying bronchial hyper responsiveness in such patients remain unclear. It could be explained either by an innate predisposition to PIBO in children who have previously (prior to the diagnosis) had a phenotype of airway hyper reactivity[14], while the small caliber of the airways in young children makes it difficult to assess bronchodilation in PFTs, or by acquired airway hyperreactivity later in the disease. There may be persistent airway hyperresponsiveness secondary to complex damage of bronchiolar functioning which includes chronic inflammatory process, scarring, narrowing and air trapping. But it seemed that poor response to bronchodilators increased as fibrosis progresses. Although the PFT parameters didn't achieve normality after the use of bronchodilators, it can help improve lung function in these patients. Further investigations are needed in order to research the mechanisms of airway hyper responsiveness and assess benefits of the use of bronchodilators in PIBO patients with a significant bronchodilator response.

In conclusion, the present case series study results demonstrated that pediatric patients with PIBO have an obstructive pattern of pulmonary function impairment. The FVC, FEV_1 and $MMEF_{25\%\text{-}75\%}$ all improved as they grew old, while FEV_1/FVC ratio decreased. This improvement may be mainly due to the development of lung parenchyma more than airway growth. And airway obstruction of some pediatric patients with PIBO can improve with the use of β_2 agonists. In future, larger populations and long term follow-ups are needed to validate these observations.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Jerkic SP, Brinkmann F, Calder A, Casey A, Dishop M, Griese M, Kurland G, Niemitz M, Nyilas S, Schramm D, Schubert R, Tamm M, Zielen S, Rosewich M. Postinfectious Bronchiolitis Obliterans in Children: Diagnostic Workup and Therapeutic Options: A Workshop Report. Can Respir J. 2020; **2020** : 5852827.
2. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. Paediatr Respir Rev. 2010;**11(4)** : 233-9.
3. Li YN, Liu L, Qiao HM, Cheng H, Cheng HJ. Post-infectious bronchiolitis obliterans in children: a review of 42 cases. BMC Pediatr. 2014; **14** : 238.
4. Colom AJ, Teper AM, Vollmer WM, Diette GB. Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis. Thorax. 2006; **61(6)** : 503-6.
5. Jinho Yu. Postinfectious bronchiolitis obliterans in children: lessons from bronchiolitis obliterans after lung transplantation and hematopoietic stem cell transplantation. Korean J Pediatr. 2015;**58(12)** : 459-65.
6. Colom AJ, Teper AM. Clinical prediction rule to diagnose post-infectious bronchiolitis obliterans in children. Pediatr Pulmonol. 2009; **44(11)** : 1065-9.
7. Colom AJ, Maffey A, Garcia Bournissen F, Teper A. Pulmonary Function of a Paediatric Cohort of Patients With Postinfectious Bronchiolitis Obliterans. A Long Term Follow-Up. Thorax. 2015; **70(2)** : 169-74.
8. Sisman Y, Buchvald F, Nielsen KG. Lung function and fitness in children treated for Post-infectious Bronchiolitis Obliterans. Eur Respir J. 2017; **50** : OA1763.
9. Cazzato S, Poletti V, Bernardi F, Loroni L, Bertelli L, Colonna S, Zappulla F, Timoncini G, Cicognani A. Airway inflammation and lung function decline in childhood post-infectious bronchiolitis obliterans. Pediatr Pulmonol. 2008; **43(4)** : 381-90.
10. Mosquera RA, Hashmi SS, Pacheco SE, Reverdin A, Chevallier J, Colasurdo GN. Dysanaptic growth of lung and airway in children with post-infectious bronchiolitis obliterans. Clin Respir J. 2014;**8** : 63-71.
11. Mattiello R, Vidal PC, Sarria EE, Pitrez PM, Stein RT, Mocelin HT, Fischer GB, Jones MH, Pinto LA. Evaluating bronchodilator response in pediatric patients with post-infectious bronchiolitis obliterans: use of different criteria for identifying airway reversibility. J Bras Pneumol. 2016; **42(3)** :174-8.
12. Mattiello R, Sarria EE, Stein R, Fischer GB, Mocelin HT, Barreto SS, et al. Functional capacity assessment in children and adolescents with post-infectious bronchiolitis obliterans. J Pediatr. 2008;**84(4)** : 337-43.
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J. 2005; **26(2)** : 319-38.
14. Castro-Rodriguez JA, Daszenies C, Garcia M, Meyer R, Gonzales R. Adenovirus pneumonia in infants and factors for developing bronchiolitis obliterans: a 5-year follow-up. Pediatr Pulmonol. 2006;**41(10):** 947-53.
15. Kim CK, Kim SW, Kim JS, KohYY, Cohen AH, Deterding RR, White CW. Bronchiolitis obliterans in the 1990s in Korea and the United States. Chest. 2001; **120(4)** : 1101-6.
16. Similä S, Linna O, Lanning P, Heikkinen E, Ala-Houhala M. Chronic lung damage caused by adenovirus type 7: a ten-year follow-up study. Chest. 1981; **80(2)** : 127-31.
17. Uyan ZS, Midyat L, Çakir E, Gökdemir Y, Sahin N. Azithromycin therapy in children with postinfectious bronchiolitis obliterans. Eur Respir J. 2016; **48** : PA1602.
18. Aguerre V, Castaños C, Pena HG, Grenoville M, Murtagh P. Postinfectious bronchiolitis obliterans in children: Clinical and pulmonary function findings. Pediatr Pulmonol. 2010; **45(12)** : 1180-5.
19. Eckrich J, Herrmann E, Voss S, Schubert R, Zielen S, Rosewich M. Short-Term Variation of Lung

Function and Airway Inflammation in Children and Adolescents With Bronchiolitis Obliterans. Lung. 2016;**194(4)** : 571-9.
20. Narayanan M, Owers-Bradley J, Beardsmore CS, Mada M, Ball I, Garipov R, Panesar KS, Kuehni CE, Spycher BD, Williams SE, Silverman M. Alveolarization continues during childhood and adolescence: new evidence from helium-3 magnetic resonance. Am J Respir Crit Care Med. 2012; **185(2)** : 186-91.
21. Narayanan M, Beardsmore CS, Owers-Bradley J, Dogaru CM, Mada M, Ball I, Garipov RR, Kuehni CE, Spycher BD, Silverman M. Catch-up alveolarization in expreterm children. Evidence from 3He magnetic resonance. Am J Respir Crit Care Med. 2013; **187(10)** : 1104-9.
22. Pisi R, Aiello M, Zanini A, Tzani P, Paleari D, Marangio E, Spanevello A, Nicolini G, Chetta A. Small airway dysfunction and flow and volume bronchodilator responsiveness in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015; **10** : 1191-7.
23. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, edersen OFP, Wanger J. Interpretative strategies for lung function tests. Eur Respir J. 2005; **26(5)** : 948-68.
24. Chung HL, Jang YY. Bronchial hyperresponsiveness observed in the children with postinfectious bronchiolitis obliterans: a long-term follow-up study. J Allergy Clin Immun. 2019; **143(2)** : AB217.
25. Yoo Y, Yu J, Kim DK, Choi SH, Kim CK, Koh YY. Methacholine and adenosine 5'-monophosphate challenges in children with post-infectious bronchiolitis obliterans. Eur Respir J. 2006; **27(1)** : 36-41.

Table 1. Characteristics of the study subjects

Date of birth	Age at the time of diagnosis	Sex	Race	Etiology	Mechianical ventilation at time of the injury	Allergy factors (including a history of wheezing, atopic dermatitis and family asthma history)
25 September 2003	7 years	Male	Han	Measles virus	Yes	No
21 September 2009	15months	Male	Han	Adenovirus	Yes	No
31 May 2011	14 months	Male	Han	Adenovirus	Yes	Eczema
12 December 2007	47months	Male	Han	Mycoplasma pneumoniae	No	No
18 August 2008	14months	Male	Han	Adenovirus	No	Eczema Wheezing
29 December 2011	31 months	Male	Han	Mycoplasma pneumoniae	No	No
12 December 2011	6 months	Male	Han	Unknown	Yes	No
17 July 2012	20 months	Female	Han	Adenovirus	No	Eczema
11 June 2010	24months	Female	Han	Mycoplasma pneumoniae	No	Eczema
17 August 2007	57 months	Female	Han	Adenovirus Mycoplasma pneumoniae	Yes	No

6 November 2009	13 months	Female	Han	Unknown	Yes	Eczema Wheezing
26 February 2009	8 years	Male	Han	Mycoplasma pneumoniae	No	Wheezing

Table 2. Baseline and final median PFT values

	PFT values (median) Baseline	PFT values (median) End of study	Change per year	95% CI	t	P-value
FEV_1	39.75%	57.8%	5.007%	3.463 to 6.552	6.356	<0.0001
FVC	41.6%	76.1%	8.212%	6.531 to 9.894	9.574	<0.0001
FEV_1/FVC	90.7%	77.85%	-3.537%	-5.09 to -1.984	-4.464	<0.0001
$MMEF_{25\%-75\%}$	22.2%	26.2%	1.583%	0.046 to 3.12	2.019	0.048

PFT, pulmonary function test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; $MMEF_{25\%-75\%}$, maximal midexpiratory flow velocity 25%-75%; CI, confidence interval.

Table 3. Bronchodilator responses in pediatric patients with PIBO, considering the mean percent variation and the mean absolute volume change from the previous measurement*.

Variable	BD response Baseline	BD response End of study
FEV_1(%change from previous)	23.01(3.3 to 64.6)	15.89(-4.6 to 42.8)
$MMEF_{25-75\%}$(%change from previous)	46.92(-3.6 to 67.6)	24.65(-14.1 to 72.2)
FEV_1(absolute volume change,in L)	0.15(0.03 to 0.32)	0.28(0.01 to 0.59)
$MMEF_{25-75\%}$(absolute volume change,in L/s)	0.16(-0.05 to 0.38)	0.18(-0.16 to 0.76)

PIBO, post-infectious bronchiolitis obliterans; BD, bronchodilator.*Values expressed as median (interquartile range).

Table 4. Analysis of factors with a potential effect on bronchodilator responses in pediatric patients with PIBO at the initial PFTs.

		BETA	95% CI
FEV_1 improvement rate(BD response)	FEV_1 improvement rate(BD response)		
	Age at the time of diagnosis	0.135	-0.194 ˜ 0.464
	Allergy factors	19.915	0.669 ˜ 39.161
$MMEF_{25-75\%}$ improvement rate (BD response)	$MMEF_{25-75\%}$ improvement rate (BD response)		
	Age at the time of diagnosis	-0.255	-0.752 ˜ 0.241
	Allergy factors	31.552	2.507 ˜ 60.598
FEV_1 improvement value(BD response)	FEV_1 improvement value(BD response)		
	Age at the time of diagnosis	0.000	-0.001 ˜ 0.002
	Allergy factors	0.059	-0.038 ˜ 0.156
$MMEF_{25-75\%}$ improvement value(BD response)	$MMEF_{25-75\%}$ improvement value(BD response)		
	Age at the time of diagnosis	-0.004	-0.008 ˜ -0.001
	Allergy factors	-0.010	-0.213 ˜ 0.193

PIBO, post-infectious bronchiolitis obliterans; PFT, pulmonary function test; BD, bronchodilator.

Figure 1. Chest HRCT scans of a 10-years old boy with PIBO. (A) mosaic perfusion pattern. (B) bronchial wall thickening and bronchial dilation.

Figure 2. Observed (solid lines) and predicted (dashed lines) progression of (A) FEV_1, (B) FVC, (C) FEV_1/FVC, (D)$MMEF_{25\%–75\%}$(E)FEV_1 improvement rate (BD response), (F)$MMEF_{25\%–75\%}$ improvement rate (BD response). Each colored line represents one patient. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; $MMEF_{25\%–75\%}$, maximal midexpiratory flow velocity 25%-75%; BD, bronchodilator.