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Post viral bronchiolitis obliterans in children: A rare and potentially devastating disease

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Educational aims

The reader will come to appreciate:

- Post-infectious bronchiolitis obliterans is potentially devastating disease.
- History of respiratory infection in healthy children, frequently during childhood.
- Nonreversible airway obstruction.
- Mosaic pattern on chest-computed tomography.
- Exclusion of other chronic lung diseases such as severe asthma, cystic fibrosis or ciliary dyskinesia, bronchopulmonary dysplasia, immunodeficiency, and alpha-1-antitrypsin deficiency.
- One hypothesis is it occurs as a result of damage to the respiratory epithelium, which provides professionals with a new therapeutic target on which to base their research.

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ABSTRACT

Post infectious bronchiolitis obliterans (PIBO) is a rare but severe disease in children. Several respiratory pathogens are incriminated but *adenovirus* is still the most represented. Risk factors are well described: the male gender, hypoxemia at diagnosis and required mechanical ventilation. No risk factor is linked to the newborn period. The clinical spectrum of PIBO is broad, ranging from asymptomatic patients with fixed airflow obstruction to severe respiratory insufficiency requiring continuous oxygen supplementation. Diagnosis includes a combination of a clinical history, absence of reversible airflow obstructions and ground glass and gas trapping on high resolution computed tomography. PIBO is primarily a neutrophilic pathology of small bronchioles characterized by high levels of pro-inflammatory cytokines leading to tissue remodeling and fibrosis of the small airways. The difficulty is to discriminate between the host's normal response, an exaggerated inflammatory response and the potential iatrogenic consequences of the initial infection treatment, particularly prolonged mechanical ventilation. Damage to the respiratory epithelium with a possible link to viral infections are considered as potential mechanisms of PIBO. No specific management exists. Much remains to be done in this field to clarify the underlying mechanisms, identify biomarkers, and develop clear monitoring pathways and treatment protocols.

INTRODUCTION

Bronchiolitis obliterans (BO) is an irreversible chronic obstructive pulmonary disease associated with obstruction and/or obliteration of the distal airways [1,2]. The most frequent causes of BO in children are post-infectious BO (PIBO), post-lung transplant BO, and post-bone marrow transplant or hematopoietic stem cell transplant BO. The mechanisms leading to the distal obstruction

Abbreviations: BO, Bronchiolitis obliterans; PIBO, Post infectious bronchiolitis obliterans; ADV, *Adenovirus*; MP, *Mycoplasma pneumoniae*; RSV, Respiratory syncytial virus; HRCT, High resolution computed tomography; FEV1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; LCI, Lung clearance index; MRI, Magnetic resonance imaging; BAL, Bronchoalveolar lavage; FeNO, Exhaled nitric oxide fraction; ICS, Inhaled corticosteroids; MBL, Mannose-binding lectin; CAR, Coxsackie and Adenovirus Receptor.

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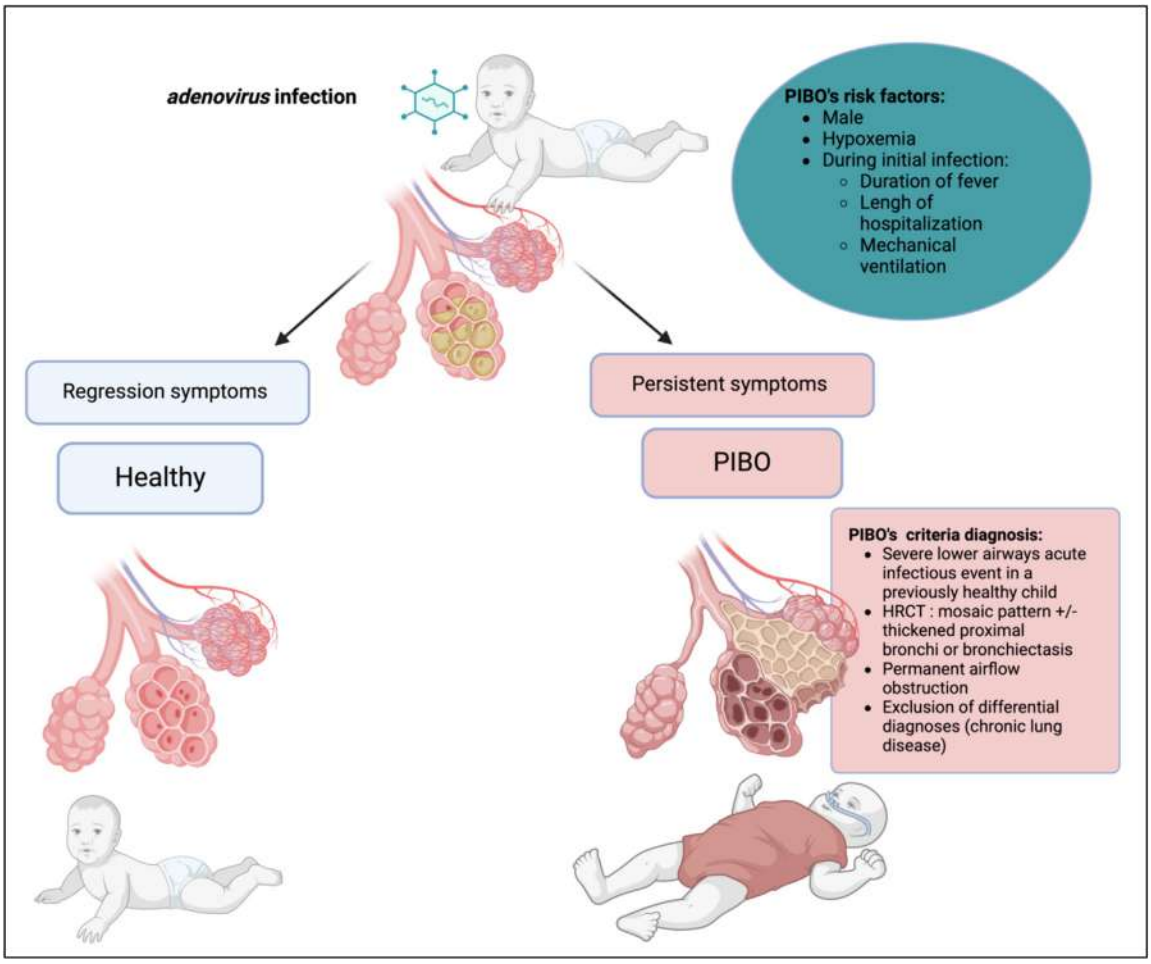

Fig. 1. Clinical symptoms of children's PIBO (post infectious bronchiolitis obliterans) with risk factors for post adenovirus infection. Created with BioRender.com.

may be different according to the cause, however the final histopathological features are the same. PIBO is characterized by inflammation and fibrosis of the terminal bronchioles leading to narrowing and/or complete obstruction of the airway lumen. Usually, these changes are related to an initial microbial aggression after an acute infectious event of the lower airways [1]. Several respiratory pathogens, including *adenovirus (ADV)* or *Mycoplasma pneumoniae (MP)* have been associated with PIBO. Currently, there are no effective treatments to improve or restore the respiratory health of PIBO patients. Therefore, there is an urgent need for a vigorous research effort to better understand the disease, potential mechanisms and triggers leading to established PIBO.

This review will examine risk factors for PIBO and the current diagnostic criteria (Fig. 1). Further, it will discuss the current state of knowledge with an emphasis on the potential role of the respiratory epithelium in this disease. Finally, the current management of PIBO is considered.

RISK FACTORS FOR PIBO

PIBO is an orphan disease. The exact incidence and prevalence are unknown, particularly in Europe. The most common form of PIBO in children occurs following a severe lower respiratory tract infection. In seven case control studies, the risk factors for developing PIBO included: male gender, the occurrence of a pleural effusion, hypoxemia at diagnosis, lactate dehydrogenase level and the requirement for mechanical ventilation. No significant association was found between the duration of fever or the length of hospitalization [3].

Geographic origin and gender

PIBO has been reported to be more common in certain populations in the Southern Hemisphere (Argentina, southern Brazil, Uruguay, Chile, New Zealand and Australia) and Koreans, pointing to genetic factors. They may play a central role in the initiation or escalation of the inflammatory process [4,5]. Ethnic characteristics have been suggested as a predisposing factor for the development of PIBO. Higher frequency of PIBO was reported in male compared to female patients. Other host conditions such as innate immunity have not yet been thoroughly assessed.

Cause of respiratory infection

PIBO is commonly associated with infection such as *ADV, MP, respiratory syncytial virus* (*RSV*), *influenzae*, *parainfluenza*, *measles* and *varicella* virus [6–8]. Few cases were described post-*SARS-CoV2* with a severe initial acute infection [9–11]. *Rhinovirus* infection was not reported as a risk factor for PIBO. However, the major virus involved in PIBO development is *ADV,* specifically serotypes 3, 7, 11 and 21 [6,12]. The viral species and the management of the initial event are found to be important in the further development of PIBO. Thus, comparing BO to controls, *ADV* and the mechanical ventilation requirement were found to contribute independently for PIBO [8]. No significant difference in gender, clinical manifesta-

tion and atopy were reported when clinical characteristics of *ADV* induced PIBO were compared with non-*ADV* linked PIBO. But a longer duration of hospital stays, mechanical ventilation time requirement and higher LDH, IL-8 and IFN-γ blood levels were found in the post-*ADV* population [13]. Variable results have been found in studies concerning young age as a potential crucial risk factor, but it is probable that immature host immunity resulting in poor immunology responses against respiratory pathogens might favour the development of PIBO [3].

DIAGNOSIS OF PIBO

The major issue is that there is no unique, widely accepted definition. Frequently, PIBO is described as a childhood disease characterized by persistent airway obstruction unresponsive to bronchodilator therapy with imaging evidence of small airway involvement [4]. The clinical spectrum of PIBO is broad, ranging from asymptomatic patients with fixed airflow obstruction to severe respiratory insufficiency requiring continuous oxygen supplementation. The diagnosis of PIBO is difficult and establishing prognosis is a lengthy process since asthma and other non-specific lung conditions are often the preferred diagnoses. The diagnosis of PIBO combines a clinical history, dyspnea and non-reversible airflow obstruction and ground glass and gas trapping on high resolution computed tomography (HRCT), however lung pathology remains the reference [4]. Diagnosis criteria are resumed in Table 1.

Symptoms and physical examination findings

There is no specific symptom of PIBO. However, tachypnea, cough, wheezing, exercise intolerance and hypoxemia persisting for at least 6 weeks after a severe lower airways acute infectious event, in a previously healthy child, should evoke the diagnosis. It may occur that the initial event is non-severe, with no acute respiratory failure but persistence of respiratory symptoms without free interval is evocative, particularly in infants. In older children, PIBO may mimic severe uncontrolled asthma. Clinical examination reveals non-specific signs of hyperinflation and wheezing and/or crackles with a permanent airflow obstruction [4].

Clinical investigations

At the respiratory functional level, spirometry generally reveals an obstructive ventilatory disorder with no or poor response to inhaled bronchodilators, with sometimes a decrease in airway obstruction and air trapping for up to 24 h after a single dose of tiotropium without clinical improvement [14]. Plethysmography revealed hyperinflation and air trapping by an increase in residual volume and an increase in functional residual capacity [1,4]. However, spirometry in very young children with PIBO is not feasible due to limited co-operation. Systematic reviews and *meta*-analyses showed a decrease in the levels of pulmonary function parameters (forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) and diffusion capacity of carbon monoxide) and with positive bronchodilator responses in children (response ranged from 30 % to 83 %) [15]. Changes in respiratory function are described in the section on morbidity and mortality.

The lung clearance index (LCI) could also be of use for diagnosis [16]. Indeed, a prospective study shown that LCI concordance indices were significantly correlated with air-trapping lung volume percentage on HRCT. This suggests that LCI is a feasible and complementary tool for assessing children with PIBO [17].

The plain chest x-ray is typically normal and should be avoided except in the case of an acute event. HRCT without contrast administration is the gold standard and plays a central role in the diagnosis of PIBO in children. Several studies and one review of PIBO in children described all radiological damage on CT with 96 % having bronchiectasis, 78 % bronchial wall thickening, 66 % atelectasis, 58 % mucus plugging and 88 % mosaic lung attenuation due to air trapping [18–20]. The discovery of mosaic lung attenuation on HRCT in a child with a typical history is a strong predictive factor of PIBO. A study comparing PIBO to difficult asthma patients found significantly higher scan scores in the PIBO group for decreased inspiratory attenuation, mosaic pattern, expiratory air trapping and bronchiectasis. But the authors also noted an overlap between the spectrum of clinical, functional, radiological and atopic characteristics of patients with PIBO and those with asthma [21]. The usual pattern depicted heterogenous areas of patchy hypo and hyperdensities called mosaic lung which reflects a variation in pulmonary alveolar density (Fig. 2). This lower density is linked to two main mechanisms: alveolar hyperinflation secondary to complete and incomplete bronchiolar obstruction, and hypoxic vasoconstriction secondary to a redistribution of blood flow to the "healthy" lung. When the disease is advanced, thickened proximal bronchi or bronchiectasis are frequently seen.

At an early stage, expiratory slides may be helpful to support an early diagnosis of BO, however it is difficult to perform in young subjects. In the post-transplant BO in children, Siegel et al. suggested that the addition of expiratory sections increases the sensitivity to 100 % and the specificity to 71 % for air trapping [22]. Contrast administration may be important in the event of a suspicion of associated pulmonary arterial hypertension or when a lung transplant is being considered [4].

Few studies reported improvement in all radiological findings except peri bronchial thickening after associated treatment with steroid and azithromycin [23]. No study on the benefit and performance of imaging during exacerbations has been conducted.

Colom et al. proposed a BO-score based on points devoted to various variables: a typical clinical history (defined as a previously healthy infant, with a severe episode of bronchiolitis and subsequent chronic respiratory hypoxemia for more than 60 days) (four points), *ADV* proven infection (three points), and HRCT scan with mosaic perfusion (four points) (Table 2). A score greater than or equal to 7 predicted the diagnosis of PIBO with a specificity of 100 % and a sensitivity of 67 % [24]. This score is not a gold standard but it is the only proposed score for diagnosis of PIBO without histopathological analysis.

Lung magnetic resonance imaging (MRI) has attracted interest in pediatric imaging, particularly given the absence of radiation [25]. But its access is difficult with the need for general anesthesia for the youngest children. Additionally, structural lung imaging

Table 1
Diagnosis criteria of post-infectious bronchiolitis obliterans in children

Severe lower airways acute infectious event in a previously healthy child.
Non-reversible airway obstruction.
High resolution computed tomography (with expiratory views if possible): mosaic pattern ± thickened proximal bronchi or real bronchiectasis.
Exclusion of differential diagnoses (chronic lung disease): severe asthma, cystic fibrosis, ciliary deficiency, bronchopulmonary dysplasia, immune deficiency or α1-antitrypsin deficiency.

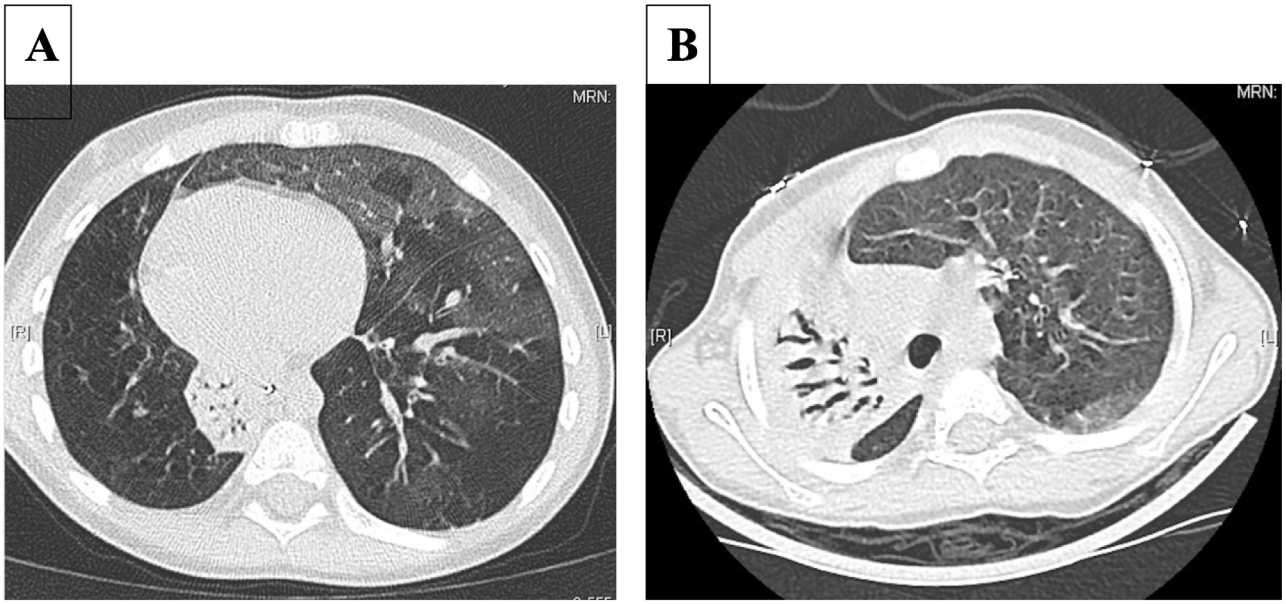

Fig. 2. High resolution computed tomography (HRCT). Representative images of the lung from children's PIBO post adenovirus [5]. (A) Lower right lobe bronchiectasis with mosaic pattern and alveolar hyperinflation. (B) Mosaic pattern on expiratory slides.

Table 2
BO-score for diagnosis of PIBO without histopathological analysis by Colom et al. [24].

Variables	Points
Typical clinical history	4
Adenovirus infection	3
High resolution computed tomography with mosaic pattern	3

with MRI is difficult due to the low signal-to-noise ratio and lower spatial resolution compared to HRCT [4]. In lung TC99 scintigraphy, reduced pulmonary perfusion was noted, such as for dual energy computed tomography [19]. Preliminary studies in animals and adults showed the benefit of positron emission tomography/computed tomography (PET/CT) in assessing the severity of pulmonary fibrosis [26,27].

Potential additional investigations

It is commonly accepted that before starting any treatment, the diagnostic work-up should include fiberoptic endoscopy with samples including bronchoalveolar lavage (BAL) [4]. BAL allows a large microbiological and cytological analysis to investigate inflammation and endobronchial biopsies are used to investigate proximal airway inflammation and structural changes. Few studies explored cytology in BAL and most of the data showed neutrophilic alveolitis and a small increase of lymphocytes [28].

Open lung biopsy is considered to be the gold standard for the diagnosis of BO. The description usually depicts bronchiolar infiltration by inflammatory cells associated with elements of tissue remodeling and fibrosis with disappearance of the small airways. The biopsies are not always contributive because of the heterogeneity of inflammation, structural changes and lack of expertise of the pathologists leading to a reduction in their diagnostic performance [4,29].

Few studies have analyzed the sputum in children with PIBO. Patients with BO had significantly higher counts of total cells and an increase in the neutrophils in induced sputum. Moreover, all pro-inflammatory neutrophilic related biomarkers (IL-1ß, IL-6, and IL-8) except TNF-α and NFκB were significantly increased in patients with BO as compared to the non-affected control group [30].

A non-invasive approach to measure exhaled nitric oxide as a marker of airway inflammation could be considered. Exhaled nitric oxide fraction (FeNO) could be clinically useful but more importantly for identifying future risk of exacerbation, as in asthma [31]. In children's asthma, contradictory results were found about relationship between FeNO and adherence with inhaled corticosteroid (ICS) [32–34]. A study comparing children with BO (including 6 PIBO) versus control subjects showed that the control group had significantly higher FeNO levels than patients with BO [30].

PATHOGENESIS OF PIBO

Several authors reported that the natural history of PIBO is highly variable and cannot be predicted for each patient [35]. The difficulty is to discriminate between the host's normal response, an exaggerated inflammatory response and the potential iatrogenic consequences of the initial infection treatment, particularly prolonged mechanical ventilation.

First, the physiopathology of the initial viral infection is not yet well described. For viral bronchiolitis, the immune response elicited by *RSV* may be both protective and deleterious. Evidence suggests the relative balance between type 1 and type 2 helper T cells responses to antigenic stimulation and the profile of evoked chemokines and cytokines determines the extent of acute *RSV* disease expression. At present, direct cytotoxic injury induced by the virus and a robust host inflammatory response contribute to the pathogenesis of acute *RSV* bronchiolitis, although the balance and chronology of the two different events are uncertain [36]. Then, the main mechanism of BO development could be linked to an initial damage to the airway epithelium leading to fibroblastic proliferation [4,35]. This hypothesis is strongly supported by Rollins et al., who observed, in adult patients with inflammatory (cellular) *MP* bronchiolitis, extensive damage of the respiratory mucosa, with loss of cilia and peribronchiolar fibrosis [37]. The typical patterns of PIBO were luminal obliteration by fibroconnective tissue and scattered lymphocytes with preserved smooth muscle wall [4]. Few findings on the damage of the bronchial epithelium were found in the literature in children's PIBO. In post-transplant BO, the lack of a normal healing by club cells and club cell secretory protein (CCSP) was reported [38].

Biological markers

BO is primarily a neutrophilic pathology of small bronchioles characterized by high levels of pro-inflammatory cytokines leading to tissue remodeling and fibrosis of the small airways [30,39,40]. No eosinophilic inflammation was found in BAL cellular content. Mistchenko et al. found high expression of ICAM-1 and high serum values for IL-6, IL-8 and TNF-α associated with the severity of *ADV* infection on hospitalized children [39]. In a prospective study enrolling patients with PIBO, patients followed for BO post hematopoietic stem cell transplant and control subjects, the authors found that the levels of neutrophils, IL-8 and calprotectin was significantly higher in BO patients compared to control subjects in induced sputum. They reported a positive correlation between the level of calprotectin in sputum with IL-8 level and neutrophil content, and pulmonary function tests such as, FEV1, maximum expiratory flow rate at 25 % vital capacity and LCI. In serum, calprotectin was significantly decreased in BO patients compared to controls [40]. In another study, Costa et al. reported no difference in IFN-γ, IL-4 and IL-10 blood levels between PIBO and healthy controls. The authors suggested that a host Th1/Th2 immune response is not associated with PIBO [41]. Serum YKL-40 levels were explored to distinguish exacerbations of PIBO from acute bronchiolitis in young children. Serum YKL-40 levels were significantly increased in the children admitted with acute exacerbation of PIBO and had a positive correlation with the severity of the disease [42]. A recent review reported the importance of distal airways in chronic airways disease with an evidence of innate and adaptive immune mechanisms. This review suggested important roles for viral and bacterial microbiome in chronic airways disease [43]. However, at present, there is no data concerning the microbiome in patients with PIBO.

Genetic markers

Few studies have been specifically designed to explore the genetic component of PIBO. The potential role of mannose-binding lectin (MBL), which is a plasma protein playing a central role in innate immunity, has been investigated. Low levels of circulating MBL were associated with more frequent and severe respiratory infections, particularly in infants aged 6–17 months before specific immune protection was established by the adaptive immune system. From a genetic point of view, MBL2-deficient variants had been reported to be associated with respiratory infections in childhood and a marker of severity in children with cystic fibrosis or ciliary dyskinesia. In a study on children with post-*ADV* PIBO, "insufficient" MBL variants were significantly more frequent in PIBO children than in controls. These patients were more severe at the time of the initial acute episode with the need for intensive care unit support and mechanical ventilation compared to "sufficient" MBL patients. The authors did not find differences in the distribution of MBL2 variants between children with and without viral characterization [44]. Selective and non-selective gene expression studies revealed differentially expressed fibrosis and apoptosis genes in patients with BO [45]. There is a need to decipher the potential for biological genetic and epigenetic markers' contributions to PIBO development.

POTENTIAL INVOLVEMENT OF RESPIRATORY EPITHELIUM IN PIBO

The respiratory epithelium is at the interface between the host and his environment and there is increasing solid evidence that this tissue plays a key role in balancing subsequent repair and inflammation [46]. Respiratory infection, particularly *ADV*, is the main cause of PIBO. Adenoviruses use mainly remarkably diverse attachment receptors, five of which have been studied structurally in the context of *ADV* binding: Coxsackie and Adenovirus Receptor (CAR), CD46, the glycans GD1a, polysialic acid and desmoglein-2 [47]. CAR was expressed at tight junction in epithelial cells and facilitated immune cell transepithelial migration [48]. CAR is a member of the junctional adhesion family and immunoglobulin superfamily and functions as a cell to cell adhesion molecule through homophilic interactions in trans. CAR-deficient airway epithelium showed significantly reduced pro-inflammatory cytokine release, neutrophil migration and *peri*-bronchial inflammation following in mice exposed to house dust mite. In human epithelial cells, depletion of CAR resulted in increased basal permeability and reduced barrier integrity [48]. CD46 is also described as a functional cellular receptor for *ADV*, but its contribution to infection by *ADV* serotypes 3 and 7 is controversial [49,50]. It has been demonstrated that ICAM-1 was expressed on the basal surface and ICAM-2 was expressed on the apical and lateral surfaces on the bronchial epithelial cells [51].

In another form of BO, donor CCSP AA and AG polymorphisms were associated with a greater risk of BO [38]. The mechanisms of apoptosis are also interesting to study given the hypotheses of remodeling abnormalities with an altered epithelial-mesenchymal transition. PANoptosis plays a key role in viral infection. Different pathways including pyroptosis, apoptosis and necroptosis are explored. These findings highlight how virus-induced PANoptosis must be balanced to reduce excessive inflammation while retaining antiviral functions. These studies indicated that activation or suppression of PANoptosis may be therapeutically targeted to improve viral infection outcomes in the future [52]. Serum caspase-1 and IL-18 receptors were measured by ELISA and compared between children with PIBO, children with a history of *influenzae* infection within the previous month without PIBO and healthy children. Caspase-1 was higher in the PIBO group and *influenzae* group; IL-18 receptor was higher in the PIBO group. These results suggested that inflammasome activation may have a role in fibrosis [53]. Thus, the epithelial damage induced by virus infection associated with the epithelial immune response would play a role in modulating the secretion of inflammatory mediators and subsequent tissue remodeling and could be involved in PIBO (Fig. 3).

CARE AND EVOLUTION OF PIBO

No specific management guidelines exist. The clinical disease may evolve for months to years after the initial pneumonia or severe respiratory illness. The potential treatments in children's PIBO are resumed in Table 3.

Early intervention

Inhaled and systemic corticosteroids are used for anti-inflammatory purposes to alter the proliferation and activation of lymphocytes, although studies do not clearly establish a benefit. Obviously, it may be necessary to start treatment early to avoid an occurrence of bronchiolar fibrosis [54]. Indeed, the duration of inflammation after the development of PIBO is important to be considered to optimize management [55]. A study of 21 children with PIBO followed for 8 years had shown an increased neutrophilic inflammation in BAL samples which was persistent over the follow-up period, indicating persistent inflammation [56]. Depending on clinical evolution, the most used treatment consists of administering boluses of methylprednisolone for 3 days consecutively at monthly intervals (generally for 3 to 6 months), as for the treatment of diffuse interstitial pneumonia [57]. Few studies evaluated corticosteroid pulses in PIBO. A retrospective study by Yoon

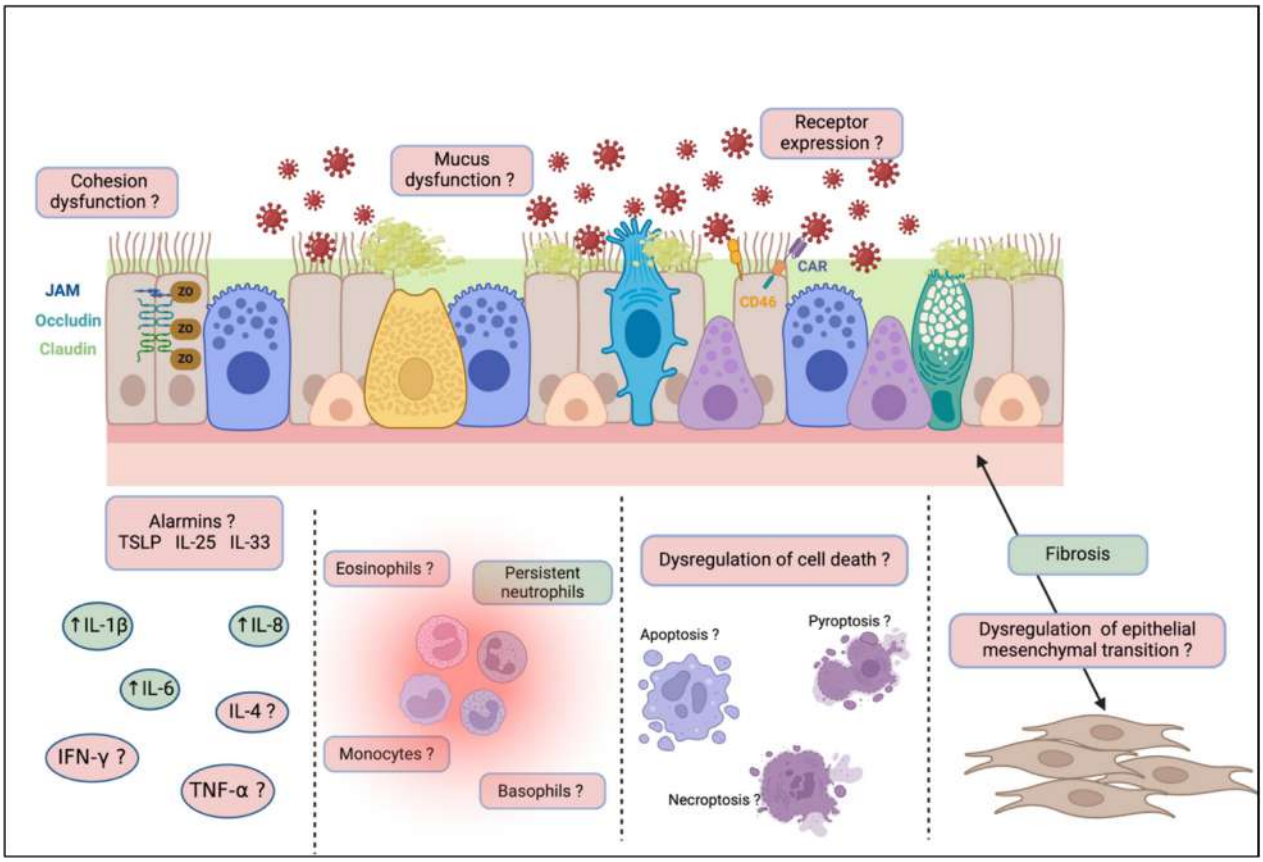

Fig. 3. Proven and probable pathogenesis of children's PIBO post adenovirus infection: the hypothesis of epithelial damage. Green rectangles correspond to data described in studies although few data were proven about cytokines secretions or persistent neutrophils and the fibrosis in histopathology. The red rectangles correspond to data which are not yet described in studies. Hypothesis about respiratory epithelium involvement such as cohesion or mucus' dysfunction, level of receptor expression, dysregulation of PANoptosis or epithelial mesenchymal transition are assumed. Created with BioRender.com.

Table 3
Potential treatments in children's PIBO.

Treatments		Level of evidence[a]
Anti-inflammatory	Inhaled corticosteroids	B
	Systemic corticosteroids	B
	AzithromycinMontelukast	DD
Anti-cytokines	Biotherapies	?
Supportive care	Oxygen	?
	Nutritional statusPulmonary rehabilitation	??
Transplantation	End-stage respiratory failure	B

[a] Level of evidence defined by the French National Authority for Health Level of evidence and gradation of good practice recommendations (2013) [79].

et al., in PIBO children treated with corticosteroid pulses, found a responders' group who had significantly thickened bronchial wall before treatment, a shorter median interval between the initial acute episode and the beginning of the treatment and a younger age at the time the pulse started [58]. Some reported cases speculate that an early intervention with corticosteroid pulses may be effective in improving the clinical course of PIBO [12,59]. However, only one study followed PIBO children treated at an early stage with corticosteroid pulses due the initial severity, hypoxemia requiring oxygen or prolonged use of oral corticosteroids. It was found to reduce airway hyperreactivity, frequency of the wheezing exacerbations and hospitalization [60]. New prospective controlled studies are needed to confirm the efficacy of pulsed methylprednisolone courses for the treatment of PIBO. Oral corticosteroids and an elongated course of systemic corticosteroid should be avoided since this is associated with severe side effects and complications including osteoporosis, bone fractures and infections [61].

Frequently, an ICS and azithromycin are currently suggested in combination. Oral azithromycin is recommended based on previous studies in obstructive bronchial diseases [54]. Zheng et al. reported for PIBO in remission an improved lung function and relief for airway obstruction, especially with a continuous ICS treatment [62]. No randomized controlled study has been carried out in children monitored for PIBO. Observational studies with combination treatment azithromycin, ICS and montelukast or acetylcysteine [23,63,64,8] were found to provide some clinical and functional benefit (spirometry and HRCT).

Additional symptomatic therapies

Oxygen should be administered in the detection of hypoxemia with pulsed oximetry value under 92 % to obtain values above 92 % or 94 % depending on the presence of an associated pulmonary arterial hypertension [65]. Non-invasive ventilatory support must be discussed if there is chronic hypercapnic respiratory insufficiency or associated weight loss [66]. In a cohort of PIBO, Bosa et al. found 21 % malnourished associated with low muscle reserves and lower Z-score predicted in 6-minute walk tests. These results emphasize the need for nutritional intervention [67]. In the PIBO we did not find any data on pulmonary rehabilitation, but data exists in patients suffering another BO. Choi et al.

found an improvement in VO2 peak and 6-min walk distance after 8-to-12-weeks of pulmonary rehabilitation in 4 cases of post-hematopoietic stem-cell transplant BO [68]. At last, the treatment of the initial viral episode might be of interest to prevent its mediate severity and the occurrence of PIBO. For instance, a randomized double-blind placebo-controlled trial investigated Dupilumab for the treatment of hospitalized patients with moderate to severe *Covid-19*. No significant difference was found concerning mechanical ventilation at day 28 between the two groups [69].

Final resort

Lung transplantation remains a treatment option for children with PIBO with end-stage respiratory failure and with an increased risk of death [70].

MORBIDITY AND MORTALITY

PIBO has a low mortality rate but the highest morbidity rate is observed during initial infection, in particularly after *ADV* [71,72]. A retrospective study of paediatric patients with BO found no death in PIBO versus 2 deaths in post-hematopoietic stem-cell transplant BO in 20 years [73]. During follow-up, children with PIBO may encounter exacerbations, particularly in the first years, often requiring hospitalization due to secondary respiratory infections [74]. No risk factor for exacerbation has been described. In another study, patients required frequent re-admission due to recurrent respiratory infections, and hypoxemia improved slowly over time [75]. During follow-up, Frolich et al. found reduced peak aerobic capacity in PIBO compared to healthy controls [76], confirmed with a systematic review [77]. It is important to investigate the exercise tolerance in children with PIBO to anticipate potential difficulties and best manage them.

The prognosis is variable, probably depending on the age of occurrence during the natural lung growth, although most will continue to have symptoms. Several studies found persistent long-term impairment of respiratory function, suggesting a persistent after effect [54,55]. Jerkic et al. showed a constant impaired pulmonary function up to 8 years of follow-up with average loss of FEV1/FVC by 1.44 % per year. In the same way, a study after a 12-year follow-up period found pulmonary function remained severely impaired that slowly improved during childhood [75]. An unequal growth of lung parenchyma over the airways suggested dysanaptic growth [29,75,78]. The management of PIBO patients requires continuous follow up beyond adolescence.

CONCLUSION

The criteria suggesting PIBO are: 1) history of respiratory infection in healthy children, frequently during childhood, 2) obstruction of the airway with no or poor response to the treatment with bronchodilatation, 3) mosaic pattern on chest-computed tomography, 4) exclusion of other chronic lung diseases. Much remains to be done in this area to clarify the underlying mechanisms, identify biomarkers, develop monitoring pathways, and clear treatment protocols. Further multi-center research studies are needed to better understand the epidemiology, pathogenesis, management and long-term outcomes. Possible dysfunction of epithelial or genetic polymorphisms predisposing to development could be defined in research methodology that may have therapeutic implications.

FUTURE RESEARCH DIRECTIONS

- Bronchial epithelium dysfunction contribution to PIBO development.
- New prospective controlled studies are needed to confirm the efficacy of pulsed methylprednisolone courses for the treatment of PIBO
- The potential for biological genetic and epigenetic markers as predictors of PIBO development.

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