ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REVIEW ARTICLE

Postinfectious bronchiolitis obliterans in children: the South American contribution

Jose A. Castro-Rodriguez (jacastro17@hotmail.com)[1], Veronica Giubergia[2], Gilberto B. Fischer[3], Claudio Castaños[2], Edgar E. Sarria[4], Ramiro Gonzalez[5], Rita Mattiello[4], Luis E. Vega-Briceño[6], Patricia Murtagh[2]

1.Pulmonology Unit, Departments of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile
2.Pulmonology Department, Hospital de Pediatria Dr Juan P. Garrahan, Buenos Aires, Argentina
3.Department of Pediatrics, Universidade Federal de Ciencias da Saude, Porto Alegre, Brazil
4. Centro Infant- Instituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brasil
5.Department of Pediatrics, Clinica Las Condes, Santiago, Chile
6.Department of Pediatrics, Clinica Alemana, Universidad del Desarrollo, Santiago, Chile

Keywords
Adenovirus, Bronchiolitis obliterans, Children, Chronic lung disease, South America

Correspondence
Jose A. Castro-Rodriguez, MD, PhD, Lira 44, 1er. Piso, casilla 114-D, Santiago, Chile.
Tel: +(56) 2 354 8189 |
Fax: +(56) 2 354 8122 |
Email: jacastro17@hotmail.com

Received
22 December 2013; revised 18 April 2014; accepted 12 May 2014.

DOI:10.1111/apa.12689

ABSTRACT

Postinfectious bronchiolitis obliterans (PIBO) is an infrequent chronic lung that causes irreversible obstruction and, or, obliteration of the smaller airways. This review particularly focuses on more than 30 studies from South America.

Conclusion: The initial PIBO event occurs in the early years of life and is strongly associated with adenovirus infection and the need for mechanical ventilator support. Treatment requires a multidisciplinary strategy. Multicentre studies are needed to determine progression, optimal management and long-term follow-up.

INTRODUCTION

Bronchiolitis obliterans is an infrequent form of chronic lung disease leading to the obstruction and, or, obliteration of the distal airways (1,2). These pathologic processes are secondary to severe chemical, infectious or immunologic insults, which lead to varying degrees of inflammation. Bronchiolitis obliterans implies a chronic necrotising and ultimately fibrosing and scarring process affecting the distal airways, which results in their progressive obliteration with resultant obstructive lung disease (3). Bronchiolitis obliterans is of special importance in paediatric recipients of allogeneic bone marrow or lung transplantations (1). A recent study from Austria reported that 52.6% of patients were found to be free from bronchiolitis obliterans 5 years after a lung transplant (4). However, bronchiolitis obliterans following a severe lung infection in children, namely postinfectious bronchiolitis obliterans (PIBO), has progressively been reported since the 1970s (5–8).

Most reports of PIBO come from Australia (7), North America (6,8), South America (9–12), Western and South Eastern Europe (13), South Korea (8,14), Taiwan (15), Malaysia (16) and New Zealand (17). In relation to South American countries, a large number of cases have been reported over the last two decades (9–12). Presently, the Bronchiolitis Obliterans in Latin America (BOLAT) initiative estimates that there are more than 700 cases of PIBO in the region (18).

This paper reviews the relevant literature in respect to epidemiology, risk factors, diagnosis, imaging, lung function, treatment and prognosis of PIBO, highlighting the South American contribution.

AETIOLOGY AND EPIDEMIOLOGY

Although PIBO in children is considered a rare condition, the prevalence found after severe viral lower respiratory tract infection (LRTI), particularly to adenovirus (AV), in young children is high. There have been reports of PIBO secondary to measles, *Mycoplasma pneumoniae*, influenza, parainfluenza, respiratory syncytial virus (RSV)

Key notes

- Postinfectious bronchiolitis obliterans (PIBO) is an infrequent chronic lung that causes irreversible obstruction and, or, obliteration of the smaller airways and this review particularly focuses on studies from South America.
- The initial PIBO event occurs in the early years of life and is strongly associated with adenovirus infection and the need for mechanical ventilator support and multidisciplinary treatment.
- Multicentre studies are needed to determine progression, optimal management and long-term follow-up.

and varicella (10,14,19). However, AV seems to be the leading cause of PIBO worldwide, associated with high mortality rate (8,9,11). Specific AV serotypes such as AV3, AV7 and AV11 were the most commonly found in South America (20); AV3 and AV7 were also common in the Asian regions (21).

The first study, from 1984 to 1986, on the aetiology of acute LRTI involving 1003 Argentinean preschoolers who required hospitalisation showed that viruses were the main cause, and after RSV, AV was the second most prevalent pathogen (22). A collaborative study from Argentina, Chile and Uruguay performed from 1984 to 1994, analysing 537 AV strains isolated from nasopharyngeal aspirates of children reported that 63% of the strains belonged to the subspecies B, 36% to C and 0.7% to E (AV4). The most frequent and serious AV isolated variants in south cone of South America were 7, 21 and 5 (20,23). This high predominance of subspecies B has not been observed in studies from other parts of the world (24,25).

A worldwide study reported that AV7 was the most frequent serotype, isolated in 59% of cases. After using restriction enzymes analysis, five different genomic variants were identified: 7b, 7c, 7h, 7i and 7j. Both 7b and 7c were similar to the variants already found in other areas (26). On the other hand, AV7h, AV7i and AV7j were new genomic variants reported from Argentina, undetected in any other study (27).

AV7h was the most frequent serotype circulated in Argentina, with 85% of all isolates representing this strain, and has been associated with the most severe and fatal cases. It circulated throughout an entire 10-year surveillance period, from 1985 to 1995, becoming the predominant variant replacing the AV7c, which circulated until 1985. Even more, AV7h was the only serotype isolated in the years 1988, 1990, 1993 and 1994, and it was last detected in May 2005 (27). Subjects studied had positive nasopharyngeal aspirates for AV by indirect immunofluorescence using monoclonal antibodies directed against the hexon protein, which has a sensitivity of only 65%. Therefore, it is likely that the real frequency of AV in the population of children with acute LRTI is underestimated.

In a study of more than 3000 Chilean infants hospitalised due to acute LRTI, 12.6% were AV positive (28); the AV7h strain was associated with more severe and fatal cases. Studies from Chile and Argentina among infants hospitalised with LRTI due to AV reported a death rate up to 15% and the development of PIBO up to 40% (9,11). There is a high prevalence of viral infections in people of low socio-economic status, because such condition is correlated with poor sanitation, unhygienic practices, indoor smoking and overcrowding, which probably contribute to the transmission of viral diseases, particularly AV. However, it has not been clearly demonstrated that low socio-economic status increased the risk of PIBO (29).

Immunological conditions of the host are also important to consider. For example, a study carried out in Israel demonstrated that serotypes of subgroup B of AV were found to be approximately four times more prevalent among immuno-compromised children than among healthy ones (30).

Fortunately, the worldwide incidence of PIBO seems to have been dropping since the beginning of the 21st century. It is likely that changes in specific AV serotype circulation might explain this decrease better than improvements in socio-economic conditions. In other parts of the world, the AV circulation is also changing. In South Korean, from 1990 to 2007, the most common serotypes were AV3 and AV7 (31). Although AV7h outbreaks were more frequent in the first years of the study period, the number of cases progressively diminished, to the point of not identifying any case over the last 2 years of surveillance. Conversely, AV3 became more prevalent with frequent outbreaks in Korea and a stable number of cases in the second half of the study period and the most severe cases of LRTI were due to AV7h (14). Fortunately, at this point, no PIBO epidemic is expected in our region. However, the study of the disease is still relevant to many children and young people who carry the consequences of PIBO.

RISK FACTORS

A case–control study involving 109 Argentinian children who developed PIBO and 99 controls found that those with AV infection were more likely to develop PIBO when compared to other viruses, including RSV, influenza and parainfluenza. In their multivariate logistic regression analysis, AV infection and mechanical ventilation were the strongest risk factors for developing PIBO (10). In a prospective study of 45 hospitalised Chilean infants with AV pneumonia followed for 5 years, those patients who developed PIBO, identified by high-resolution computed tomography of the chest, (HRCT-C) were more likely to be admitted to intensive care, undergo mechanical ventilation and need supplemental oxygen, systemic corticosteroids and albuterol than those who were not developed PIBO. A study from Argentina in 415 children hospitalised with AV-positive LRTI reported that among those 150 who developed PIBO, the risk factors were hospitalisation for more than 30 days, multifocal pneumonia and hypercapnia. Independent risk factors for death in the acute stage of disease were as follows: mechanical ventilation, multifocal pneumonia, hypercapnia, coagulopathy, neurological symptoms and co-infection with measles (11).

Ethnic factors have also been suggested as a predisposing factor. A preliminary report on genetic profiles found that PIBO Argentinian patients had an increased frequency of HLA-DR8-DQB1*0302 haplotype, which is frequent in the Amerindian population (32). In contrast, in a study from Porto Alegre, Brazil, 70% of the PIBO children followed up were Caucasian (33). Other racial distributions may be found according to local ethnic composition.

PATHOGENESIS AND HISTOPATHOLOGY

Characteristic histopathology lesion of PIBO is the pattern of constrictive bronchiolitis, in which bronchiolar walls are

partially or completely replaced by inflammation and fibrosis leading to partial or total occlusion of the airway lumen. Other common bronchiolar findings include mucus stasis, airway distortion and dilation/bronchiectasis, and inflammatory exudates (3). Even though factors such as ischaemia, reperfusion and infection likely play a role in the molecular and cellular changes observed in PIBO, the host immunologic response might also contribute to the severity of pulmonary infection as well as the subsequent development of bronchiolitis obliterans.

A Chilean study showed that unlike RSV, AV infections elicit an intense Th1 response during the infecting period which is maintained while the virus is still present, leading to an intense inflammatory response (34). Argentinean patients with severe AV pneumonia have been shown to have immune complexes containing AV antigen in the lung, as well as increased serum levels of interleukin-6 (IL-6), IL-8, and tumour necrosis factor-alpha (TNF-α) (35,36). A study from Brazil has provided evidence that the pathogenesis of childhood PIBO involves B and T lymphocytes (37). CD3+ T cells were the cells most frequently found in pulmonary biopsy tissue of patients with PIBO, with a predominance of the CD8+ T cell subtype. CD8 cells can activate alveolar epithelial cells to produce chemokines, thereby increasing inflammation and contributing to the perpetuation of injury in the lungs.

Studies, from Italy and Korea, evaluating bronchoalveolar lavage (BAL) fluid of patients with PIBO have shown an elevated percentage of neutrophils as well as a slight increase in IL-8 concentration. Neutrophils products are directly cytotoxic to endothelial and epithelial cells, and these include proteolytic enzymes, such as elastase and collagenase (38,39). Therefore, airway CD8+T cells as well as neutrophils may play an important role in sustaining peripheral airway damage and fibrotic remodeling after severe infection.

It is not clear whether children with PIBO have persistent small airway inflammation. It was postulated that viruses can produce an abnormal immunologic setting for an autoimmune-like response (37). Histopathological reports have demonstrated signs of active and persistent inflammation in the small airways, even years after an episode of acute pulmonary insult (38). Latent infection by AV could stimulate connective-tissue growth and amplify the inflammatory process (37). Additional examination of the persistence of AV-DNA in the lungs could further elucidate the aetiology and highlight the pathogenic mechanisms of the disease (40). Unfortunately, it is not clear why some types of AV cause massive long-term damage, while other types or other respiratory viruses with similar pathogenesis features do not. More studies need to be performed to solve this crucial issue.

Characteristic lesions of PIBO are patchily distributed throughout both lungs without any definite pattern. Therefore, open lung biopsy is not recommended due to the difficulties in obtaining an adequate sample. Some believe that the presence of inflammation identified by histologically or by BAL fluid suggests that PIBO is a progressive disease. Recently, a Chilean study found evidence of a significant increase in oxidative stress in the BAL fluid of children with PIBO post-AV infection (40), which indicates inflammatory activity as suggested in cellular studies. Surprisingly, adequate antioxidant activity was also present in BAL fluid, which indicates a counterbalance of the oxidative effects. This would hint at the fact that the disease is not progressive, as was recently describe in stabilisation of lung function at adolescence period, personal communication. Moreover, a study revealed that lymphocyte predominance found in the BAL fluid of some PIBO patients was different from post-transplant bronchiolitis obliterans patients, which is well known to be progressive. In PIBO, the CD3+ T cells predominate with the CD4/CD8 ratio in the lower limit; while in post-transplant bronchiolitis obliterans, the CD8+ T cells predominate, which are capable of releasing toxic compounds (38).

CLINICAL MANIFESTATIONS AND PROGNOSIS

Postinfectious bronchiolitis obliterans is characterised by the presence of signs and symptoms of severe and persistent small airway obstruction; however, there are no specific signs and symptoms of PIBO and a wide spectrum of clinical manifestations can be observed in studies from South America (9,11,40). The severity and extent of lung lesions vary greatly, which may contribute to under diagnosis. However, despite ethnic and geographic differences, there were similar clinical findings between Korean and North American patients (8).

The clinical presentation of the initial infection depends on the interaction between the host's immunological status and response, and the characteristics of the infecting microorganism. The initial event is a severe acute bronchiolitis/pneumonia with severe tachypnea, cyanosis, respiratory distress and multiorganic compromise, in children under 3 years of age leading to high oxygen requirements, admission to the intensive care unit and sometimes mechanical ventilatory support (9–11). Progression to PIBO may occur, with increasing dyspnoea, chronic wheezing, cough and sputum production. Children may have a dependence on the use of long-term ventilator or oxygen treatment at home.

Wheezing, hypoxaemia and crackles can persist for months to years. Another pattern is frequent wheezing with symptom free intervals. Many patients progress to recurrent pneumonia, recurrent or chronic atelectasis, wheezing exacerbations and cor pulmonale, thoracic deformity and clubbing (9,18,41). Pneumonia and secondary bacterial infections contribute to the development of bronchiectasis that may become saccular. After 2–3 years, the symptoms ameliorate and exacerbations are milder and less frequent (42). At school age, exercise capacity is reduced and respiratory muscle function impaired (43). In the most severe cases, the symptoms persist into adolescence, with chronic cough, bronchorrhea, wheezing and rarely a spontaneous pneumothorax. In some patients, lung function may be severely reduced and oxygen therapy necessary,

leading to a poor quality of life. These patients are candidates for lung transplantation.

Mortality can be as high as 18% from acute AV infection, but, once a diagnosis of PIBO is established, the mortality rate is low (9,11). However, morbidity is high in cases of frequent hospitalisations due to respiratory infections with variable degrees of airway obstruction during the first 2 years of age (16). There is a relative improvement in terms of frequency and intensity of these exacerbations in subsequent years, although without an improvement in lung function and radiological status (41). Proposed explanations include ongoing alveolarisation of lung areas unaffected by the initial injury and overall airway growth with increased lumen area.

Health-related quality of life data from patients revealed scores comparable to healthy peers, suggesting that children with PIBO may cope well with the disease (44). As in most chronic lung diseases, a more rapid decline of lung function in PIBO patients compared with healthy adults should be expected. An Italian study described a decline in forced expiratory volume in one second (FEV_1) of 1% per year in children which correlated well with the inflammatory profile found in the BAL fluid (38). In contrast, imaging studies from Japan suggest that there is a clear progression of the lesions only during the first 3 months after the initial insult without signs of subsequent deterioration in the following 2 years (45). A study carried out in Brazilian and Chilean children with PIBO reported that those with the severest imaging findings in HRCT obtained within the first 2 years of the acute event had worse lung function a decade later (46). This suggests that those who show a functional decline are the ones with more severe forms of the disease, and whose progression could also be explained by their inherent co-morbidities and complications, such as bronchiectasis or lobar collapse (41).

DIAGNOSIS AND FOLLOW-UP

Histological examination of adequate lung biopsy remains the most accurate method to diagnose PIBO (1–3). However, transbronchial biopsy often results in a small sample size, with a decreased likelihood of obtaining adequate numbers of small airways for examination, and is not considered risk-free. Therefore, the technique is not regarded as very useful for diagnosis. On the other hand, open lung biopsy has higher morbidity and complication rates (41). In difficult cases or unusual presentations, it must, however, be considered as a diagnostic tool. The search for less invasive methods to diagnose PIBO constitutes one of the major challenges faced by clinicians caring for patients at risk. The clinical instability of patients increases the risk of lung biopsy complications, and the patchy distribution of the lesions makes adequate sampling challenging. Therefore, the diagnostic pathway combines clinical and imaging criteria, particularly HRCT-C, with laboratory testing for virus identification, as well as ruling out other forms of chronic lung disease (12,18).

A clinical prediction index to diagnose PIBO was recently published (48). Its development, however, was based only on the study of patients with severe forms of the disease. Therefore, validation of the index in other centres as well as in patients with less severe forms of the disease is necessary. A different criterion, drawn from the consensus of expert opinions, is commonly used for diagnosis, Table 1, (18).

Imaging

There are no pathognomonic imaging features of PIBO, but radiology plays an important role in diagnosis and follow-up. The three commonly used imaging methods are HRCT-C, conventional chest radiographs (CXR) and lung ventilation/perfusion (V/Q) scans. HRCT-C is the most sensitive of the three, identifying parenchymal and airway abnormalities in large and small airways (49,50). The most characteristic tomographic finding in PIBO is a mosaic pattern of lung attenuation, with reduced vascularity in the lucent areas due to abnormal ventilation, air trapping and secondary hypoxic vasoconstriction, Fig. 1A,B. Other tomographic findings include bronchiectasis, air trapping, bronchial wall thickening, atelectasis and mucus plugging (18). Compared with CXR or V/Q scans, a critical limitation of HRCT-C is the radiation exposure. Lower dose protocols are increasingly used, but the safety of even these levels of radiation is not completely certain. New equipment and imaging methods have been developed and could be used in PIBO cases for both diagnosis and follow-up. The combined use of Xenon or Helium-3 in HRCT-C and magnetic resonance studies are two examples where good quality images as well as functional information can be obtained with low or no radiation exposure (51).

Table 1 Criteria used to approach diagnosis of postinfectious bronchiolitis obliterans in children

1. History of an acute and severe bronchiolitis/viral pneumonia in previously healthy children in the first 3 years of life, especially if treated in intensive care unit, prolonged hospitalisation or ventilated
2. Evidence of persistent airway obstruction after the acute event, identified either by physical examination, especially long-term crackles. Lung function tests will show airway obstruction that is unresponsive to bronchodilators or only partially reactive along time. If there remain some doubts to the diagnosis, a 2-week course of systemic corticosteroids and inhaled albuterol may be tried
3. Chest radiograph findings of obstructive lung disease such as hyperinflation, atelectasis, airway thickening and bronchiectasis
4. Mosaic pattern, bronchiectasis and air trapping in chest computed tomography, especially if unresponsive to position change or between inspiratory and expiratory exposition
5. Exclusion of other chronic progressive lung diseases might be relevant in some cases and clinicians must rethink the diagnosis periodically. Differential diagnosis includes the following: tuberculosis, cystic fibrosis, bronchopulmonary dysplasia, immunodeficiencies, problematic severe asthma and alpha-1-antitrypsin deficiency. Most of these may be suspected on a clinical basis

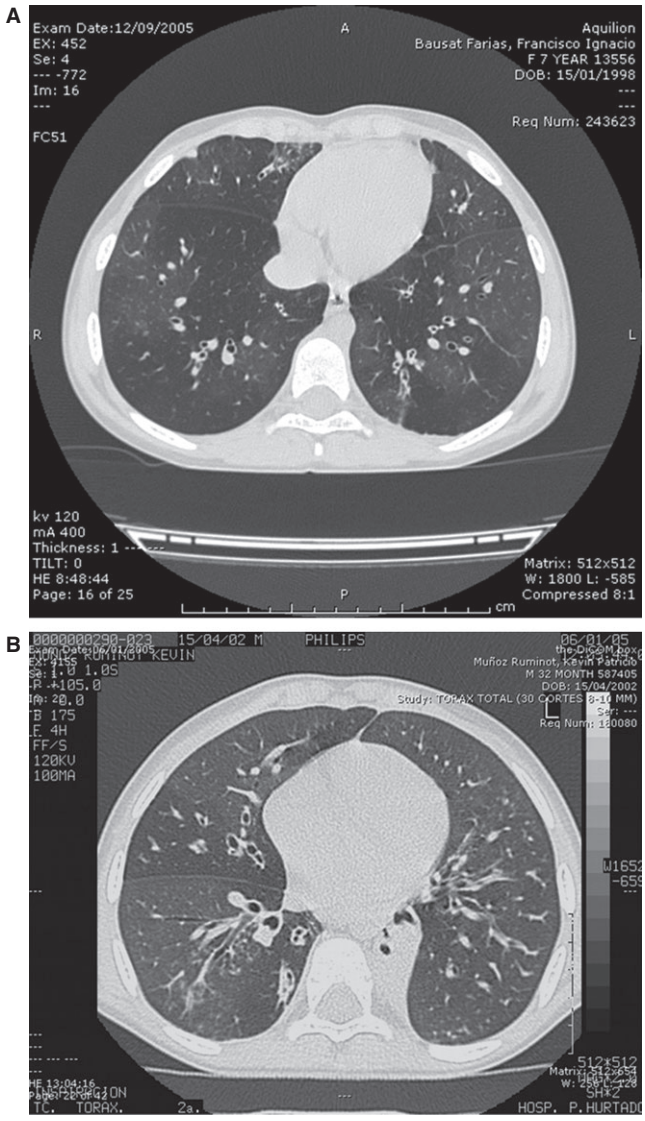

Figure 1 (A) High-resolution computed tomography of the chest in a 7-year-old boy with postinfectious bronchiolitis obliterans (PIBO). Note the presence of minor bronchiectasis and the mosaic pattern of lung attenuation. (B) High-resolution computed tomography of the chest in a 3-year-old boy with PIBO. Note the severe presence of bronchiectasis, air trapping, bronchial wall thickening, atelectasis and mucus plugging in both lungs.

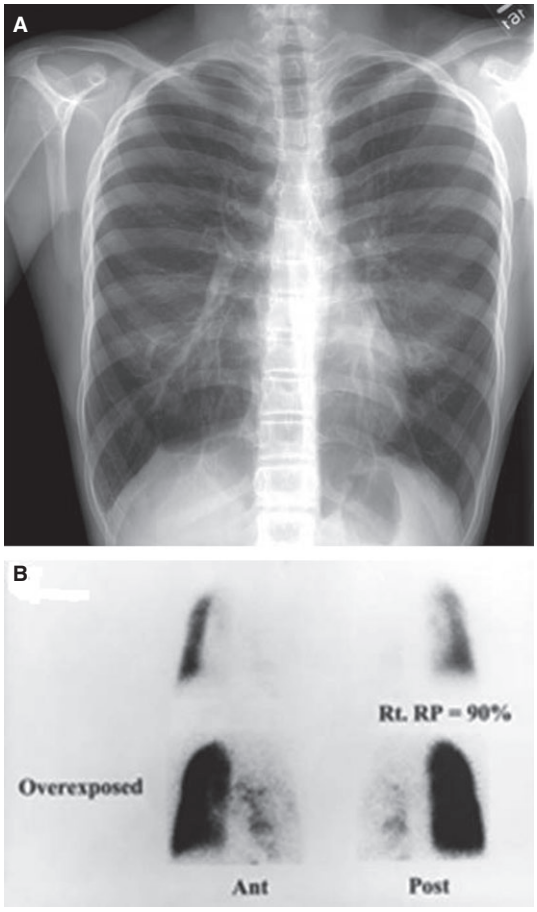

Figure 2 (A) Chest X-ray in 12-year-old child with postinfectious bronchiolitis obliterans (PIBO). Note the peri-bronchial thickening and air trapping. (B) Scan ventilation/perfusion (V/Q) in 4-year-old child with PIBO. Note the severe mismatch V/Q and exclusion of the left lung.

Chest radiographs is the primary imaging modality used in PIBO. The most common findings are peri-bronchial thickening and air trapping. Air trapping may be generalised or localised; straight diaphragms and retrosternal air are also indirect signs of air trapping, Fig. 2A. Atelectasis and bronchiectasis may also be present (7). CXR are commonly used in the follow-up of children with PIBO on as-needed basis to confirm or exclude complications during exacerbations such as focal infections or atelectasis or to monitor the evolution of existing lung sequelae. V/Q scans provide the overall distribution pattern of the compromised areas of the lung. Matched V/Q defects are seen, which can have a segmental, subsegmental or lobar distribution, Fig. 2B. Although V/Q scans are more accurate than CXR, but less than HRCT-C in detecting impaired areas, they are not considered to be a good diagnostic tool (48).

Pulmonary function testings

Pulmonary function testing (PFT) is an important tool for the overall diagnosis as well as the follow-up of paediatric patients with PIBO. Where infant pulmonary function laboratories are available, test like rapid thoracic compression techniques should be performed as soon as the infant's clinical status allows it; unfortunately, those laboratories are few in Latin America. It is important to emphasise that these children are sick and often hypoxic; therefore, the mandatory sedation of the infant may be risky. Typically, infants have a severe and fixed airflow obstruction, decreased compliance and increased resistance with little if any response to albuterol (52). This impairment seems to persist unchanged during the first 2 years of life. In the preschool years, lung function seems to follow the clinical course, with a slow improvement in the obstructive

component, probably due to lung and thoracic wall development.

A recent study in Brazilian and Chilean children showed no differences in z-scores for forced vital capacity (FVC), but an increase in two z-scores for expiratory flow at 25–75% of the forced vital capacity ($FEF_{25–75}$) over time (12). However, significant lung function impairment is one of the hallmarks of the disease, directly associated with the degree of damage to the small airways. Studies from South America, Portugal and Korea have shown that, although there may be a differences regarding racial background and viral serotypes, PIBO is an obstructive lung disease characterised by mild to moderate reduction in FVC and significant reduction FEV_1, FEV_1/FVC and $FEF_{25–75}$ (12,21,53,54). It is worth mentioning that $FEF_{25–75}$ showed the most severe reduction. The reduction in FVC should not be assumed to be an indication of restriction; it is an effect of the dramatic obstruction present in PIBO cases, Fig. 3.

Plethysmography supports spirometry and imaging, demonstrating significant increases in lung volumes and airway resistance, both a characteristic of obstruction. Increased residual volume and total lung capacity (TLC) are consistent with air trapping and hyperinflation (12,21). When patients become adults, hyperinflation might be more frequent due to changes in the mechanical properties of the lungs.

The forced oscillation technique, or one of its variants, is a practical alternative to measure airway resistance, even in small children. In a Chilean study, children with PIBO and a mean age of 5.6 showed a significant increase in resistance in the IOS (9), similar to their older counterparts using plethysmography. Some debate exists regarding the bronchodilator response to be expected in cases of PIBO, which may vary from case to case (9,12,41,55). The response, however, will never be complete, because the histological hallmark demonstrates irreversible obstructive changes in PIBO (3).

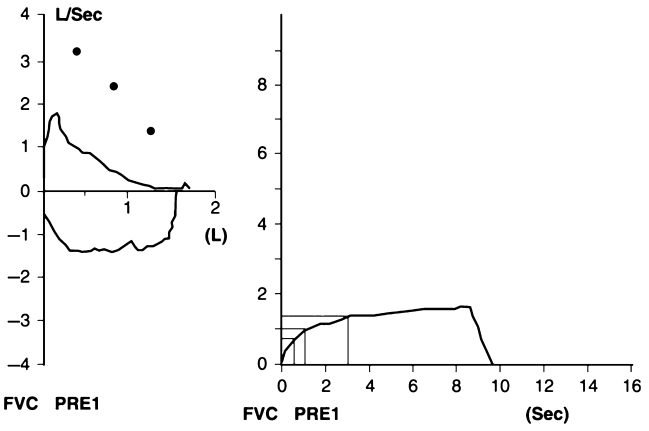

Figure 3 Spirometry findings of a 10-year-old child with postinfectious bronchiolitis obliterans (with Dr. Fischer's permission).

Cardiovascular assessment

Most children and adolescents with PIBO participate in normal activities with their peers, including physical activities. This, however, does not mean that formal exercise testing will produce normal results. A study in Brazilian children and adolescents showed a reduced exercise capacity in 6-min walk testing (6MWT) and cardio-pulmonary exercise testing (CPET) (43). Distance walked during the 6MWT and peak oxygen consumption estimated during CPET was significantly reduced compared with healthy peers. Not surprisingly, lower CPET but not 6MWT correlated well with lower FEV_1 and higher residual volume (RV)/TLC. When available, CPET should be performed periodically during follow-up. Even though the 6MWT is a low cost test, it should not be considered a full substitute of CPET, and only could be an alternative for institutions lacking of CPET (47). However, the question of how these tests could change the management of PIBO is a matter of further investigation.

TREATMENT

Recently, Chilean guidelines for diagnosis and management involving a multidisciplinary approach were published (56). Data on the treatment are scarce, and thus, therapeutic decisions may not be based on evidence (57). All treatments need to be supportive and several different aspects of the disease should be managed. Successful approaches to other chronic lung diseases have been tried, including treatment by a multidisciplinary team. General preventive measures, such as vaccination against *Streptococcus pneumoniae* and influenza and avoidance of exposure to active or passive smoking, should be adopted.

After the initial injury, many patients may develop respiratory failure and require oxygen therapy for periods of at least four to 6 months. Oxygen saturation should be above 94% at all times and the fraction of inspired oxygen titrated to maintain this saturation can be obtained through portable oxygen concentrators. Clinical improvement leads to complete weaning from oxygen in most cases. In an Argentinian study, 87% of 117 patients who developed PIBO required oxygen supplementation after discharge for a median period of 33 months (11). Saturation should be measured at different times during the day and overnight during sleep. Pulses of systemic corticosteroids in the initial injury have been used in some centres. However, this treatment needs to be test in randomised trials.

Patients with PIBO usually develop bronchiectasis. Accordingly, respiratory physical therapy for the mobilisation of secretions to minimise chronic inflammation of the airway and to decrease recurrent infections is necessary. Antibiotics are likely required in most exacerbations. Considering the chronic bronchial obstruction essentially fixed the cardinal feature of the disease, the utility of albuterol is little. However, some children are more responsive than others (9,21). Corticosteroids are frequently used in clinical practice. However, their use for the treatment of PIBO is controversial because no clinical

studies have confirmed their efficacy. Clinical improvement and reduction in symptoms have sometimes but not always been reported. Some children are more responsive than others and have some degree of bronchial hyper-reactivity. A study carried out in Portugal showed that PIBO and problematic severe asthma had identifiable characteristic features, but overlapping values may turn them undistinguishable (52). Macrolides have been postulated as a possible treatment because of their anti-inflammatory and immune-modulatory effects. A recent Argentinean trial showed no significant differences in lung function or number of pulmonary exacerbations between azithromycin and placebo during 6 months of treatment (58). New biological treatments such as anti-TNF-alpha need to be tested (19).

Pulmonary rehabilitation may have a role in improving overall respiratory muscle function; further studies using this approach are necessary. Lung transplantation is indicated in patients with severe forms of the disease (extremely impaired pulmonary function tests and oxygen dependency).

A nutritional plan should be developed by analogy with other chronic obstructive pulmonary diseases. Moderate and severe forms of PIBO warrant referral to a nutritionist to help the child achieve the best possible physical growth. Adequate nutritional support should compensate for the greater caloric requirement resulting from increased respiratory work. There are few studies in the literature stressing the specific importance of nutritional care in PIBO (33). Another possible consideration is depletion of vitamin D due to PIBO. There are recent studies showing associations between vitamin D levels and chronic respiratory conditions (59). However, no studies on vitamin D depletion involving PIBO have yet been published.

A prospective study to assess the nutritional status of 28 Brazilian children and adolescents with PIBO demonstrated that 43% had malnutrition or were at risk of malnutrition (33). Muscle bulk measured by muscular circumference was low in 61% patients. And there was a negative correlation between results in the 6MWT and findings of malnutrition and low muscle reserve. Pubertal status must be taken into account. Fat distribution and muscle bulk must also be evaluated.

FUTURE DIRECTIONS

Identification and treatment of patients with PIBO may be facilitated using a new validated clinical score that considered the whole spectrum of the disease. As the number of study participants is usually small, multicentre studies should be conducted to better understand issues such as the inflammation process associated with the disease, different risk factors or the best treatment approaches. The treatment requires a multidisciplinary strategy and a multicentre approach to address the challenges in terms of defining the molecular pathology, improving care and optimising long-term outcome. Considering the use of new biological treatments is important. Pulmonary lung rehabilitation and nutritional programmes for children and young adults who have sequels due to PIBO are mandatory. It is also possible that using experience drawn from treatments in post-transplant bronchiolitis obliterans will help children with PIBO.

CONCLUSION

Postinfectious bronchiolitis obliterans is an infrequent chronic lung disease secondary to a severe viral infection with irreversible obstruction and, or, obliteration of the smaller airways. The initial event occurs in early years of life and is strongly associated with AV infection and the need for mechanical ventilatory support. The diagnosis is reached through a combination of clinical, radiological and laboratory data. Treatment requires a multidisciplinary strategy. Despite the South American experience and contribution with more than 30 published papers described in Table S1, providing important clue to the understanding of PIBO, more multicentre studies are needed to determine disease progression, optimal treatment and ensuring best practice in long-term follow-up, including the transition to adult clinics.

COMPETING INTEREST

None to declare.

FUNDING

None.

References

1. Kurland G, Michelson P. Bronchiolitis obliterans in children. *Pediatr Pulmonol* 2005; 39: 193–208.
2. Hardy KA, Schidlow DV, Zaeri N. Obliterative bronchiolitis in children. *Chest* 1988; 93: 460–6.
3. Mauad T, Dolhnikoff M. Histology of childhood bronchiolitis obliterans. *Pediatr Pulmonol* 2002; 33: 466–74.
4. Gruber S, Eiwegger T, Nachbaur E, Tiringer K, Aigner C, Jaksch P, et al. Lung transplantation in children and young adults: a 20-year single-centre experience. *Eur Respir J* 2012; 40: 462–9.
5. Becroft DM. Bronchiolitis obliterans, bronchiectasis, and other sequelae of adenovirus type 21 infection in young children. *J Clin Pathol* 1971; 24: 72–82.
6. Penn CC, Liu C. Bronchiolitis following infection in adults and children. *Clin Chest Med* 1993; 14: 645–54.
7. Chang AB, Masel JP, Masters B. Post-infectious bronchiolitis obliterans: clinical, radiological and pulmonary function sequelae. *Pediatr Radiol* 1998; 28: 23–9.
8. Kim CK, Kim SW, Kim JS, Koh YY, Cohen AH, Deterding RR, et al. Bronchiolitis obliterans in the 1990s in Korea and the United States. *Chest* 2001; 120: 1101–6.
9. 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: 947–53.
10. Colom AJ, Teper AM, Vollmer WM, Diette GB. Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis. *Thorax* 2006; 61: 503–6.

11. Murtagh P, Giubergia V, Viale D, Bauer G, Pena HG. Lower respiratory infections by adenovirus in children. Clinical features and risk factors for bronchiolitis obliterans and mortality. *Pediatr Pulmonol* 2009; 44: 450–6.
12. Mattiello R, Mallol J, Fischer GB, Mocelin HT, Rueda B, Sarria EE. Pulmonary function in children and adolescents with postinfectious bronchiolitis obliterans. *J Bras Pneumol* 2010; 36: 453–9.
13. Yalcin E, Dogru D, Haliloglu M, Ozcelik U, Kiper N, Gocmen A. Postinfectious bronchiolitis obliterans in children: clinical and radiological profile and prognostic factors. *Respiration* 2003; 70: 371–5.
14. Callaway Z, Kim SH, Kim JY, Kim DW, Kim C-K. Adenovirus infection with serious pulmonary sequelae in Korean children. *Clin Respir J* 2011; 5: 92–8.
15. Chiu CY, Wong KS, Huang YC, Lin TY. Bronchiolitis obliterans in children: clinical presentation, therapy and long-term follow-up. *J Paediatr Child Health* 2008; 44: 129–33.
16. Chan PW, Muridan R, Debruyne JA. Bronchiolitis obliterans in children: clinical profile and diagnosis. *Respirology* 2000; 5: 369–75.
17. Lang WR, Howden CW, Laws J, Burton JF. Bronchopneumonia with serious sequelae in children with evidence of adenovirus type 21 infection. *Br Med J* 1969; 1: 73–9.
18. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev* 2010; 11: 233–9.
19. Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr* 2008; 20: 272–8.
20. Kajon AE, Mistchenko AS, Videla C, Hortal M, Wadell G, Avendano LF. Molecular epidemiology of adenovirus acute lower respiratory infections of children in the south cone of South America (1991-1994). *J Med Virol* 1996; 48: 151–6.
21. Aguerre V, Castaños C, Pena HG, Grenoville M, Murtagh P. Postinfectious bronchiolitis obliterans in children: clinical and pulmonary function findings. *Pediatr Pulmonol* 2010; 45: 1180–5.
22. Weissenbacber M, Carballal G, Avila M, Salomon H, Harisiadi J, Catalano M, et al. Etiologic and clinical evaluation of acute lower respiratorythact infections in young Argentinian children: an overview. *Rev Infect Dis* 1990; 12(Suppl. 8): S889–98.
23. Kajon AE, Suarez MV, Avendano LF, Hortal M, Wadell G. Genome type analysis of South American adenoviruses of subgenus C collected over a 7-year period. *Arch Virol* 1993; 132: 29–35.
24. Brandt CD, Kim HW, Vargosko AJ, Jeffries BC, Arrobio JO, Rindge B, et al. Infections in 18,000 infants and children in a controlled study of respiratory tract disease. I. Adenovirus pathogenicity in relation to serologic type and illness syndrome. *Am J Epidemiol* 1969; 90: 484–500.
25. Schmitz H, Wigand R, Heinrich W. Worldwide epidemiology of human adenovirus infections. *Am J Epidemiol* 1983; 117: 455–66.
26. Li QG, Wadell G. Analysis of 15 different genome types of adenovirus type 7 isolated on five continents. *J Virol* 1986; 60: 331–5.
27. Videla C, Carballal G, Kajon A. Genomic analysis of adenovirus isolated from Argentinian children with acute lower respiratory infections. *J Clin Virol* 1999; 14: 67–71.
28. Larranaga C, Kajon A, Villagra E, Avendano LF. Adenovirus surveillance on children hospitalized for acute lower respiratory infections in Chile (1988-1996). *J Med Virol* 2000; 60: 342–6.
29. Fischer GB, Teper A, Colom AJ. Acute viral bronchiolitis and its sequelae in developing countries. *Paediatr Respir Rev* 2002; 3: 298–302.
30. Mandelboim M, Dror P, Azar R, Bromberg M, Mendelson E. Adenovirus infections in hospitalized patients in Israel: epidemiology and molecular characterization. *J Clin Microbiol* 2011; 49: 597–601.
31. Lee J, Choi EH, Lee HJ. Comprehensive serotyping and epidemiology of human adenovirus isolated from the respiratory tract of Korean children over 17 consecutive years (1991-2007). *J Med Virol* 2010; 82: 624–31.
32. Teper AM, Marcos CY, Theiler G, Colom AJ, Fainboim L. Association between HLA and the incidence of Bronchiolitis Obliterans in Argentina. *Am J Respir Crit Care Med* 2004; 169 (Suppl.): A382.
33. Bosa VL, Mello ED, Mocelin HT, Benedetti FJ, Fischer GB. Assessment of nutritional status in children and adolescents with post-infectious bronchiolitis obliterans. *J Pediatr* 2008; 84: 323–30.
34. Diaz PV, Calhoun WJ, Hinton KL, Avendano LF, Gaggero A, Simon V, et al. Differential effects of respiratory syncytial virus and adenovirus on mononuclear cell cytokine responses. *Am J Respir Crit Care Med* 1999; 160: 1157–64.
35. Mistchenko AS, Diez RA, Mariani AL, Robaldo J, Maffey AF, Bayley-Bustamante G, et al. Cytokines in adenoviral disease in children: association of interleukin-6, interleukin-8, and tumor necrosis factor alpha levels with clinical outcome. *J Pediatr* 1994; 124: 714–20.
36. Mistchenko AS, Lenzi HL, Thompson FM, Mota EM, Vidaurreta S, Navari C, et al. Participation of immune complexes in adenovirus infection. *Acta Paediatr* 1992; 81: 983–8.
37. Mauad T, van Schadewijk A, Schrumpf J, Hack CE, Fernezlian S, Garippo AL, et al. Lymphocytic inflammation in childhood bronchiolitis obliterans. *Pediatr Pulmonol* 2004; 38: 233–9.
38. Cazzato S, Poletti V, Bernardi F, Loroni L, Bertelli L, Colonna S, et al. Airway inflammation and lung function decline in childhood post-infectious bronchiolitis obliterans. *Pediatr Pulmonol* 2008; 43: 381–90.
39. Koh YY, Jung DE, Koh JY, Kim JY, Yoo Y, Kim CK. Bronchoalveolar Cellularity and Interleukin-8 Levels in Measles Bronchiolitis Obliterans. *Chest* 2007; 131: 1454–60.
40. Mallol J, Aguirre V, Espinosa V. Increased oxidative stress in children with post infectious Bronchiolitis Obliterans. *Allergol Immunopathol* 2011; 39: 253–8.
41. Zhang L, Irion K, Kozakewich H, Reid L, Camargo JJ, da Silva Porto N, et al. Clinical course of postinfectious bronchiolitis obliterans. *Pediatr Pulmonol* 2000; 29: 341–50.
42. Mocelin H, Fischer G, Iriar K, Cunha L. Long-term clinical and functional assessment of children with post-infectious bronchiolitis obliterans. *Rev Chil Pediatr* 2004; 75: 12–7.
43. 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: 337–43.
44. Mattiello R, Sarria EE, Fischer GB, Mocelin HT, Stein R. Health related quality of life of Brazilian children with post-infectious bronchiolitis obliterans. *Eur Respir J* 2009; 34 (Suppl. 53): A732s.
45. Suga K, Ishikawa Y, Motoyama K, Kume N, Matsunaga N. Irreversible long-term pulmonary functional impairments after adenovirus type-7 pneumonia: assessment with xenon-133 ventilation and Tc-99 m MAA perfusion studies. *Eur Radiol* 2000; 10: 1411–5.
46. Mattiello R, Sarria EE, Mallol J, Fischer GB, Mocelin H, Bello R, et al. Post-infectious bronchiolitis obliterans: can CT scan

findings at early age anticipate lung function? *Pediatr Pulmonol* 2010; 45: 315–9.
47. Colom AJ, Teper AM. Clinical prediction rule to diagnose post-infectious bronchiolitis obliterans in children. *Pediatr Pulmonol* 2009; 44: 1065–9.
48. Yuksel H, Yilmaz O, Urk V, Yuksel D, Goktan C, Savas R, et al. Clinical significance of lung perfusion defects in children with post-infectious bronchiolitis obliterans. *Tuberk Toraks.* 2009; 57: 376–82.
49. Soto GG, Linares PM, Díaz PJ, Escaffi JJ, Pedersen MF, Mardones CN, et al. High resolution computed tomography in children with adenoviral pulmonary sequelae: characteristics and correlations with lung function. *Rev Chil Radiol* 2002; 8: 149–53.
50. Zhang L, Irion K, da Silva Porto N, Abreu e Silva F. High-resolution computed tomography in pediatric patients with postinfectious bronchiolitis obliterans. *J Thorac Imaging* 1999; 14: 85–9.
51. Haran Jogeesvaran K, Owens C. Chronic diseases of lung parenchyma in children: the role of imaging. *Pediatr Radiol* 2010; 40: 850–8.
52. Teper AM, Kofman CD, Maffey AF, Vidaurreta SM. Lung function in infants with chronic pulmonary disease after severe adenoviral illness. *J Pediatr* 1999; 134: 730–3.
53. Bandeira T, Negreiro F, Ferreira R, Salgueiro M, Lobo L, Aguiar P, et al. Clinical, radiological, and physiological differences between obliterative bronchiolitis and problematic severe asthma in adolescents and young adults: the early origins of the overlap syndrome? *Pediatr Pulmonol* 2011; 46: 573–80.
54. Kim HY, Kwon JW, Seo J, Song YH, Kim BJ, Yu J, et al. Bronchiectasis in children: 10-year experience at a single institution. *Allergy Asthma Immunol Res* 2011; 3: 39–45.
55. Linares PM, Meyer PR, Soto GG. Evaluación de la respuesta broncodilatadora en pacientes secuelados de adenovirus. *Rev Chil Pediatr* 2004; 75: 37–44.
56. Vega-Briceño LE, Zenteno AD. Clinical guide for diagnosis and care of children and adolescents with post-infectious bronchiolitis obliterans. *Rev Chil Enf Resp* 2009; 25: 141–63.
57. Lenney W, Boner AL, Bont L, Bush A, Carlsen KH, Eber E, et al. Medicines used in respiratory diseases only seen in children. *Eur Respir J* 2009; 34: 531–51.
58. Castaños C, Salim M, Pereyra C, Aguerre V, Lucero B. *Effect of azithromycin on lung function and pulmonary exacerbation in children with post-infectious bronchiolitis obliterans*. San Francisco: ATS, 2012: p. 6131.
59. Finklea JD, Grossmann RE, Tangpricha V. Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies. *Adv Nutr* 2011; 2: 244–53.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 List of South Americans' relevant publications.