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Review Article

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Post-infectious Bronchiolitis Obliterans (PIBO): A review

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Introduction

The term "bronchiolitis obliterans" (BO) likely describes a common pathologic alteration of small airways following a variety of inciting diseases with different etiologies and characteristics.[1] The initial insult, the localized inflammatory response, and preexisting factors including nutritional status and genetic variants are felt to influence the process which finally leads to the observed pathology in small airways. There are three forms of BOs seen by the pediatricians: post-infectious bronchiolitis obliterans (PIBO), BO post lung transplantation; and BO after bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT)[2]. BO following human stem cell transplantation (HSCT), and following lung transplantation (LT) have been extensively studied and well understood. But post-infectious BO (PIBO) are difficult to study because of its sporadic appearance and low incidence.

Definition

PIBO is a process characterized by persistent airway obstruction with functional and radiological evidence of small airway involvement that is in general unresponsive to bronchodilator treatment. Postinfectious bronchiolitis obliterans (PIBO) is an irreversible obstructive lung disease characterized by subepithelial inflammation and fibrotic narrowing of the bronchioles after lower respiratory tract infection during childhood, especially early childhood.[3]

Epidemiology

Although exact incidence of PIBO in children is unknown,[4] but the prevalence of BO was estimated to be 0.6% out of 2897 autopsies and 244 lung biopsies performed at a single center diagnosed as BO.[5]

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Etiology

Viral etiologies were detected in most of the cases of PIBO.[4,6,7] The most common viruses are adenovirus, rhinovirus and respiratory syncytial virus. Other viruses are influenza, parainfluenza and measles. Among the bacteria mycoplasma pneumonia is an important pathogen causing PIBO.[8]

Risk factors

Hypoxemia has been found to be the most significant risk factor for PIBO, followed by mechanical ventilation, tachypnea, and wheezing. Use of glucocorticoids, use of gamma globulin, co-infection of bacteria, a history of wheezing, and being male may also play a role.[9] Children are at high risk of developing PIBO with severe adenovirus bronchiolitis/pneumonia treated with invasive mechanical ventilator at an early time period.[10]

Pathogenesis and histopathology

Pathogenesis of postinfectious bronchiolitis obliterans. (1) Epithelial injury is induced by lower respiratory tract infection with microorganisms such as virus or mycoplasma. (2) Epithelial cells release interleukin (IL) 8 and other proinflammatory mediators, which recruit neutrophils and other inflammatory cells to the small airway. (3) Matrix metalloproteinase (MMP) and profibrotic cytokines and mediators are released from those cells, resulting in matrix degradation, collagen deposition, fibroblast proliferation, and ultimately, peribronchial fibrosis. (4) CD8+ T cells play a predominant role in epithelial injury and chronic inflammation after viral infection. (5) Th17 cells are involved in tissue remodeling, and IL-17 induces IL-8 secretion, which is related to airway neutrophilia.[1,4]

Clinical features

The mean age at diagnosis 2.18 years with the range of 0.8-5.7 years. The mean age at injury is 1.38 years

with range 0.6-3.8 years. More male is affected than female, ratio 2.2:1. The initial presenting features are fever, cough, and tachypnea. Physical examination shows chest retractions, hyperinflation, wheeze and crackles. The mean hospitalization period 30.3 days with range 14-73 days. There is long term home oxygen therapy in some cases.[11] Other clinical features may be chest deformity, finger clubbing and decreased air entry.[6] There is no history of asthma and the disease course varies between 7 and 31 months.[12] PIBO is diagnosed by clinical criteria describing symptoms such as tachypnea, cough, wheezing, exercise intolerance and hypoxemia persisting for at least 6 weeks after severe bronchiolitis or pneumonia.[4]

Investigations

Chest radiology is abnormal in 92% cases characterized by hyperinflation, patchy ground glass opacity, bronchial wall thickening, atelectasis and bronchiectasis. HRCT is abnormal in 100% cases with the features of patchy ground-glass density, mosaic attenuation, vascular attenuation, air trapping, bronchial wall thickening, bronchiectasis and mucus plugging.[6,12]

Lung function testing in patients with PIBO presents with typical patterns. The spirometry shows an irreversible or fixed obstructive flow-volume curve with decreased forced expiratory volume (FEV1), a reduced Tiffeneau index (FEV1/VC), and end-expiratory flow (MEF25). On body plethysmography, hyperinflation and air trapping are indicated by an increased residual volume (RV) and an increased functional residual capacity (RV/TLC).[13,14,15] Spirometry primarily measures obstruction in the larger airways; however, it is a generally insensitive detector of small airway obstruction. If facilities are available, Multiple Breath Washout test may be done to detect small airway obstruction like that observed in cystic fibrosis, primary ciliary dyskinesia and chronic obstructive pulmonary disease.[16,17] Especially for the pediatric population, Forced Oscillation Technique (FOT) has the advantage over spirometry that it does not require the performance of respiratory maneuvers due to the small amplitude pressure oscillations superimposed on normal breathing.

Bronchoscopy with bronchoalveolar lavage (BAL): It is common consensus that bronchoscopy and BAL should be performed[4] to rule out persistent infection with viral, fungal and bacterial pathogens before systemic anti-inflammatory treatment is given.

Treatment

Since PIBO is a rare chronic irreversible obstructive lung disease, treatment options have not been clearly defined and there are different strategies between centers. The treatment of PIBO is empirical, and there is no accepted treatment protocol. In general, the treatment for PIBO should be a combination of optimal supportive care and anti-inflammatory therapy to impair lymphocyte proliferation and activation since inflammation plays an important role in the pathogenesis of PIBO Table-1.[18]

Table 1: *Treatment options in PIBO.*

Anti-inflammatory therapy		Supportive therapy	
(i)	Systemic corticosteroid	(i)	Supplemental O2
(ii)	Azithromycin	(ii)	Nutritional support
(iii)	Combination-therapy: FAM (fluticasone/ azithromycin/montelukast)	(iii)	Immunization (influenza/pneumococcal)
(iv)	Immunglobulin substitution	(iv)	Avoid cigarette smoke
(v)	Steroid sparing anti-inflammatory agent	(v)	Airway clearance if bronchiectasis (hypertonic saline)
(vi)	Tumor necrosis factor inhibitor	(vi)	Bronchodilators if responsive
(vii)	Rescue therapy (extracorporeal photopheresis)	(vii)	Exercise therapy/pulmonary rehabilitation

Steroid: In dependence on the clinical course, inhaled and systemic corticosteroids are used to counteract the inflammatory component. Ideally, corticosteroids should be given early during the developing disease process and before airway fibrosis is established.[14] It is common agreement that the approach of choice is pulse steroid therapy with intravenous methylprednisolone 10–30 mg/kg for 3 consecutive days and repeated monthly for 3–6 months as it is used for childhood interstitial lung disease. Oral corticosteroids and an elongated course of systemic corticosteroid should be avoided, since this is associated with severe side effects and complications like bone fractures or mortality from infections.

Azithromycin. It is well known that corticosteroids do not target neutrophilic airway inflammation efficiently. In contrast, azithromycin has been effective in controlling neutrophilic inflammation and improving lung function in various diseases such as diffuse panbronchiolitis, cystic fibrosis COPD, and BOS post-lung transplantation.[19] Although there are no RCTs in children with PIBO, oral azithromycin 10 mg/kg given three times weekly is recommended on the basis of studies in other obstructive diseases.[14] Although there are no RCTs in children with PIBO and since azithromycin is well tolerated, oral azithromycin 10 mg/kg given three times weekly is recommended as long term management on the basis of studies in other obstructive diseases.[14]

Fluticasone, Azithromycin, and Montelukast (FAM): Several studies reported that a combination of inhaled fluticasone, azithromycin, and montelukast (FAM) could be an effective treatment in patients with bronchiolitis obliterans.[20] The efficacy of FAM in PIBO is not known. Single centers have reported to use FAM as a combination therapy in PIBO. Although this treatment option is safe, no formal trials have been conducted yet.

Bronchodilator: Chronic obstructive airway disease and hyperinflation play an important role in the pathophysiology of PIBO. There is postbronchodilator changes consistent with reversibility based on FEV1 (12% increments and 200 ml) after inhalation of salbutamol.[18] Whether this is due to concomitant allergies or asthma or whether it is a symptom of a distinctive subtype of PIBO is difficult to say. Two studies reported that patients do favorably respond to long-acting muscarinic receptor antagonists (LAMAs). Interestingly the placebo-controlled trial of Teixeira demonstrated a meaningful improvement after tiotropium alone in PIBO[21] and after tiotropium plus salbuterol in BOS post- HSCT.[22] In a multicentre study with adult patients by Bergeron et al., it was revealed that there was a significant improvement in FEV1 in patients with mild to severe BOS post-HSCT after a 6-months trial of budesonide/formoterol

IVIG therapy: The role of IVIG therapy has recently been studied in the treatment of PIBO. PIBO patients showed favorable clinical and radiological responses to regular IVIG treatment, possibly due to minor immune deficiency secondary to steroids or as a result of undetected adaptive and innate immune defects involved in the etiology of severe PIBO.[23]

Conclusion

PIBO should be considered in children having persistent cough, tachypnea, wheezing and hypoxemia persisting for more than 6 weeks after an attack of severe bronchiolitis and not responding to conventional medication and evaluation found negative for asthma, pulmonary tuberculosis, cystic fibrosis, primary immunodeficiency and primary ciliary dyskinesia. The most important investigation is radiology and imaging (CXR and HRTC) which shows hyperinflation, ground glass density, bronchial wall thickening, mosaic attenuation, air trapping, bronchiectasis and mucus plugging. Treatment is empirical and there is no accepted treatment protocol. Supportive treatment includes supplemental oxygen therapy, nutritional support, immunization against influenza and pneumonia, airway clearance. Anti-inflammatory treatment comprises systematic corticosteroid, azithromycin, combination therapy FAM, immunoglobulin substitution and steroid sparing anti-inflammatory agents.

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