



REVIEW ARTICLE

Bronchiolitis obliterans in children

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Abstract

Objective: to review the literature on general aspects of bronchiolitis obliterans, with emphasis on childhood postinfectious bronchiolitis obliterans.

Methods: the most important publications on bronchiolitis obliterans were selected, using basically the Medline database (January of 1966 to September of 1999).

Results: this review is organized as follows: introduction, general aspects of bronchiolitis obliterans (terminology, histopathology and classification), and postinfectious bronchiolitis obliterans (etiological agents, clinical and radiological aspects, diagnosis and investigation, and treatment).

Comments: bronchiolitis obliterans is a clinical syndrome which is more common than previously believed in the pediatric population, thus deserving pediatricians' attention.

J Pediatr (Rio J) 2000; 76(3): 185-92: bronchiolitis obliterans, organizing pneumonia.

Introduction

In a clinical sense, bronchiolitis obliterans (BO) refers to a chronic obstructive airflow syndrome associated with inflammatory lesions of the small airways.¹ Pathologically, the term has been used to describe two types of bronchiolar lesions, that is, proliferative bronchiolitis and constrictive bronchiolitis.¹⁻³ Although the first case of BO was described a century ago,⁴ several aspects of the epidemiology, pathogenesis, effective treatment, and prognosis of this disorder remain unknown or uncertain.

Until recently, BO was considered a rare disease both in adults and in children.⁵⁻⁷ In 1941, LaDue reported one case of BO among 42,038 autopsies performed over a period of 42 years.⁸ In 1988, Hardy et al. identified 19 pediatric cases among all autopsies (n = 2,897) and pulmonary biopsies (n = 244) performed at the Saint Christopher Children's Hospital, in Philadelphia, U.S., in 25 years.⁹ In the past decades, the focus of interest in relation to this disease was shifted to the adult population (Figure 1), due to the recognition of new causal factors, such as organ transplantation.¹⁰⁻¹⁶

In children, BO is usually preceded by infection of the lower airways, caused mainly by adenovirus.¹⁷⁻²¹ Although the number of studies about BO in adults is increasing, this disease has not yet called the attention of pediatricians. This raises the question of whether the small number of reports regarding BO in children reflects the low incidence of this disease in the pediatric population or the lack of knowledge regarding the diagnosis of this disease. Currently, despite

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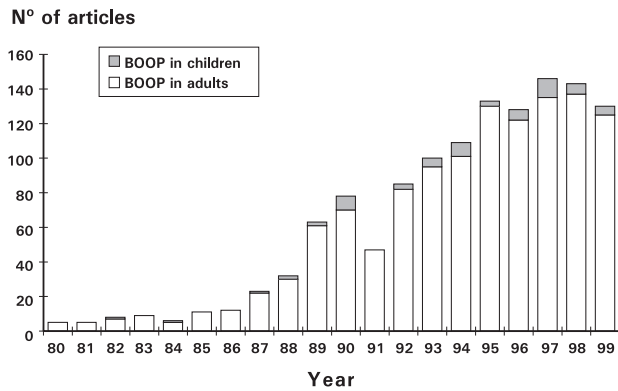


Figure 1 - Number of English and non-English articles about bronchiolitis obliterans published since 1980

the lack of epidemiological information on the prevalence of BO in children, several clinical observations suggest that this prevalence may be higher than previously thought.^{9,20,21} Zhang et al. identified 36 children with a clinical diagnosis of BO in the Pediatric Pneumology Unit at Hospital de Clínicas de Porto Alegre, Brazil, over a period of 8 years;²² this indicates that BO may account for a considerable proportion of the chronic respiratory diseases affecting children in this setting. Taking these aspects into consideration, the objective of the present study was to review the main general features of bronchiolitis obliterans, with emphasis on postinfectious bronchiolitis obliterans in childhood.

Terminology

For years, the clinical entity “bronchiolitis obliterans” has confused physicians and pathologists. This confusion originates from the fact that the term is used to describe two different types of bronchiolar lesion. In addition, it is partially due to the clinical and histopathological terms employed in the literature to characterize this syndrome.

In 1901, Lange was the first to use the term bronchiolitis obliterans in two patients with idiopathic pulmonary disease.⁴ The pathological examination of those patients showed that the bronchiolar lumen and the adjacent alveoli were filled with granulation tissue originated on the bronchiolar wall. Since then, several other terms, such as fibrous bronchiolitis obliterans, obliterative bronchiolitis, and small airways disease have been occasionally applied in the literature to identify this disease in various clinical situations.^{8,9,23-26} These terms were related to the histopathological finding of bronchiolar lumen obstruction by granulation tissue and fibrosis, with or without alveolar involvement.

In 1973, Gosink et al. applied the term constrictive bronchiolitis to some of 52 BO carriers whose obliterative lesion was restricted to the bronchioles and who did not present significant alveolar involvement.²⁷ This term was coined to underscore that the pathologic findings in those cases were different from the pathologic findings in most of the 52 patients, whose obliterative lesion affected both bronchioles and alveoli. The term was not incorporated in clinical practice, and its use was limited almost exclusively to histopathology.^{1,3,26,28}

In 1983, Epler & Colby²⁹ proposed the term bronchiolitis obliterans organizing pneumonia (BOOP) to describe the cases of bronchiolitis obliterans with alveolar involvement, in which the granulation tissue inside the bronchioles extended all the way to the alveolar ducts and alveoli. Since then, BOOP has been accepted as a clinical term in the literature.^{1,30-32}

Depending on the presence (or not) of alveolar involvement, it is obvious that the generic term bronchiolitis obliterans may refer to two different diseases, that is, BO without organizing pneumonia, and BOOP. Recently, the term bronchiolitis obliterans, or BO, has been used only to describe cases of BO with no organizing pneumonia.^{33,34} To avoid confusion, in the present article, we will use BO to refer to bronchiolitis obliterans without organizing pneumonia, and generic BO to refer to bronchiolitis obliterans in its broadest concept. Although the exact relation between BO and BOOP has not been clearly established, both have been shown to present specific clinical, radiological, physiological, and histopathological characteristics (Figure 2).

It must be stressed that in 1983, Davison et al. proposed the term cryptogenetic organizing pneumonia (COP) to identify a group of eight patients whose clinical, radiological, and pathological status was similar to that of patients with idiopathic BOOP.³⁵ There have been several debates in the literature about which would be the most adequate term to define this pulmonary disease.³⁶⁻³⁸ Until now, different authors have been using these terms interchangeably.^{39,40} Nevertheless, idiopathic BOOP is the most common term in the literature worldwide.⁴⁰⁻⁴²

Histopathological findings of generic bronchiolitis obliterans

Colby & Myers^{1,2} defined the histopathological terms that identify generic BO and also provided a detailed description of two types of bronchiolar lesions, named constrictive bronchiolitis and proliferative bronchiolitis. Constrictive bronchiolitis includes a spectrum of morphological alterations, ranging from bronchiolar inflammation and peribronchiolar fibrosis to total obstruction of the bronchiolar lumen due to submucosal scarring (Figure 3).^{1,3}

Generic bronchiolitis obliterans		
	Bronchiolitis obliterans	Bronchiolitis obliterans organizing pneumonia
Etiology	organ transplantation, idiopathic, connective tissue disease, infection, use of irritant substances	infection, connective tissue disease, drug inhalation
Histopathology	constrictive bronchiolitis	proliferative bronchiolitis
Physiology	obstructive pattern	restrictive pattern (predominantly)
Radiology	normal or pulmonary hyperinsufflation	ductal-alveolar or interstitial pattern
Response to corticotherapy	variable	good
Prognosis	unfavorable	favorable

Figure 2 - Comparison between BO and BOOP

At an early stage, constrictive bronchiolitis consists of bronchiolar epithelium necrosis and of inflammatory infiltration of the mucosa, submucosa, peribronchiolar area, and bronchiolar lumen, predominantly in the terminal bronchioles.^{1-3,26} The inflammatory infiltration has a variable number of lymphocytes, plasmocytes and neutrophils. Mononuclear cells predominate in the bronchiolar wall, and neutrophils predominate in the bronchiolar lumen.^{1,3} Frequently, the bronchioles are distorted and contain mucus plugs. In a more advanced stage, submucosal fibrosis occurs, reaching the bronchiolar lumen in a concentric pattern.^{1,26} With the progression of the fibrotic process, the bronchiolar lumen is reduced and eventually obliterated. The obliteration of the bronchiolar lumen tends to be focally located along a bronchiole, and, therefore, its identification requires serum sections.¹⁰ The color of the elastic tissue may help recognize affected airways.¹ Constrictive bronchiolitis, considered an irreversible lesion and sometimes referred to as obliterative bronchiolitis^{26,43} is the main histopathological finding in BO.¹

Proliferative bronchiolitis is characterized by granulation tissue shaped as polypoid tuft inside the airway lumen, involving predominantly the respiratory bronchioles, the alveolar ducts, and the alveoli.^{2,3,26} Granulation tissue consists of cells (fibroblasts and a variable number of macrophages, lymphocytes, neutrophils, and plasmocytes) and a matrix rich in proteoglycans. In addition to the polypoid tuft, other abnormalities may be identified in the airways.^{2,3,26,44} The most common phenomenon is the accumulation of macrophage foam cells. Sometimes, neutrophils are also found in the alveolar space. The interstice also presents significant alterations. The thickness of the

alveolar septum usually increases due to the infiltration of chronic inflammatory cells and hyperplasia of type II pneumocytes. The interstitial process is not diffuse; it is generally limited to the polypoid tuft area. Proliferative bronchiolitis is the main BOOP histopathological finding, and it is potentially reversible.¹

Classification of bronchiolitis obliterans (generic)

Until the first half of the 1970s, generic BO included only three subcategories: idiopathic BO, postinfectious BO, and BO associated with inhalation of irritant substances. As new causes and associated syndromes were recognized, the classification of generic BO became more complex.¹⁰⁻¹⁴

In 1983, Epler & Colby suggested the following clinical classification of generic BO: BO associated with the inhalation of irritating substances; postinfectious BO; BO associated with connective-tissue disease; BO associated with local lesions; and idiopathic BOOP.²⁹

In 1994, Epler³³ proposed a more comprising clinical classification for bronchiolar diseases (Table 1). In this classification, BO was categorized as a bronchiolar disease with airflow obstruction and included seven categories. BOOP was considered a bronchiolar disease with interstitial lesion, and also included seven categories.

Post-infectious bronchiolitis obliterans

In children, BO is frequently caused by respiratory infection. In theory, any type of lower airway infection could potentially cause BO; however, the most common disease triggering BO is acute viral bronchiolitis.^{20,22,45}

Table 1 - Clinical classification of bronchial diseases³³

1. Bronchiolitis without airflow obstruction
2. Bronchial diseases with airflow obstruction
Bronchiolitis (membranous bronchiolitis)
Acute bronchiolitis
Chronic bronchiolitis
Respiratory bronchiolitis in smokers
Bronchiolitis associated with mineral dust inhalation
Diffuse panbronchiolitis
Bronchiolitis obliterans (constrictive bronchiolitis)
Idiopathic
Associated with inhalation of irritant substances
Postinfectious
Associated with rheumatoid disease (connective tissue disease)
Associated with drug use
Posttransplantation
Others
3. Interstitial bronchial diseases
Respiratory bronchiolitis with pulmonary interstitial disease
BOOP
Idiopathic
Postinfectious
Associated with rheumatoid disease (connective tissue disease)
Associated with located lesion
Associated with drug use
Associated with immunologic disease
Others

Estimates show that about 1% of the patients with acute viral bronchiolitis may develop postinfectious BO.⁴⁶ The fact that acute viral bronchiolitis is the most common viral infection affecting the lower airways in infants, affecting up to 10% of the children in the 1st year of life,⁴⁷ suggests that postinfectious BO may have a strong impact on the pediatric population.

Due to the lack of published studies concerning postinfectious BO, the following review is based on case reports and on data obtained from 31 of the 36 patients regularly followed by us at HCPA.

Etiological agents: Adenovirus (types 3, 7, and 21) is the most frequent agent associated with the onset of postinfectious BO.^{17-19,45} Other viruses (respiratory syncytial virus, parainfluenza 2 and 3, influenza A and B, and measles viruses), mycoplasma, and type B streptococci were also identified as etiological agents in some cases of postinfectious BO.^{9,46,48,49} Among 31 patients at Hospital de Clínicas de Porto Alegre, three underwent a virological study during the early stage of acute viral bronchiolitis, with identification of adenovirus in the nasopharyngeal secretions of all these patients. In other five patients, pulmonary tissue obtained through biopsy was submitted to immunoperoxidase. The period between the beginning of the

disease and the biopsy varied from 2 months to 7 years. We were not able to identify the presence of viral antigens in the pulmonary tissue of these five patients.

Clinical and radiological aspects: The clinical and radiological manifestations in postinfectious BO are very heterogeneous, and depend on the severity and extension of the bronchopulmonary lesions and on the duration of the disease.²⁰⁻²² Typically, acute viral bronchiolitis will be associated with fever, cough, wheeze, and tachypnea. A physical examination will typically reveal the presence of retraction (intercostal, subcostal, and suprasternal), wheeze and fine crackles. Thorax X-rays may show peribronchial infiltration, pulmonary hyperinsufflation, and segmental or subsegmental atelectasis. Instead of the expected normalization within 1 or 2 weeks, these symptoms, respiratory signs, and radiological abnormalities remain after the first episode of acute viral bronchiolitis.

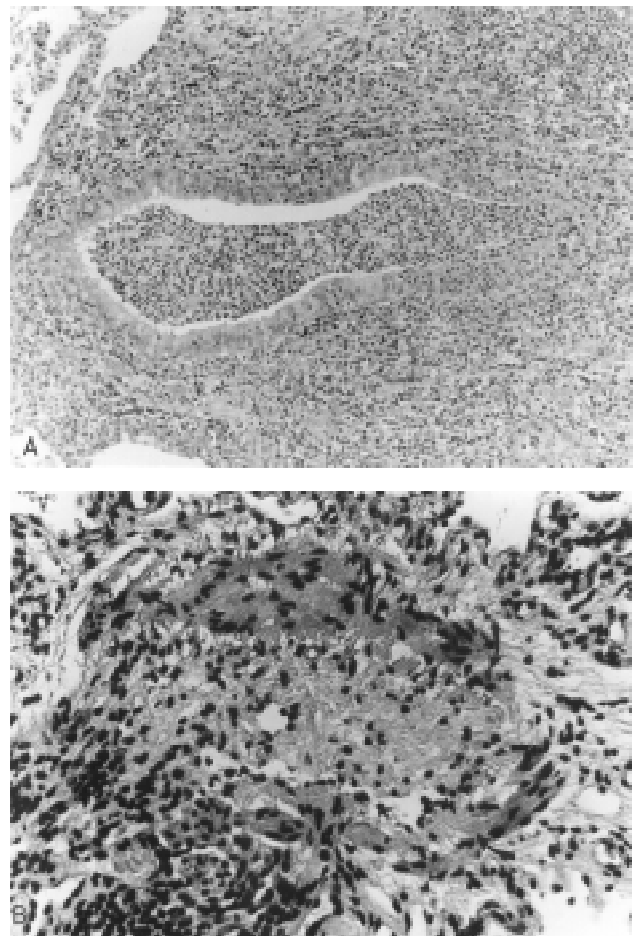


Figure 3 - Histopathological finding of constrictive bronchiolitis. **A** - Partial obstruction of bronchiole by peribronchial fibrosis; inflammatory infiltration on the wall and in the bronchiolar lumen. **B** - Complete obliteration of a bronchiole (arrows) by fibrous tissue

The clinical and radiological evolution of postinfectious BO has not been clearly defined yet. The 31 patients followed at Hospital de Clínicas de Porto Alegre (follow-up ranging from 1.6-8.3 years; average = 3.5 years) presented different clinical and radiological evolution. Three patients died of progressive respiratory failure in the first 3 years after the episode of acute viral bronchiolitis. Seven patients became asymptomatic, with normal physical examination and with minimal alterations on thorax X-rays (bronchial thickening). A clinical improvement suggested by the gradual disappearance of the symptoms and by the decrease in the intensity of respiratory signs was noticed starting at the 2nd year after the acute viral bronchiolitis episode in the remaining 21 patients, despite the persistence of some symptoms and respiratory signs (cough, retraction, wheeze and fine crackles) and of radiological abnormalities (bronchial thickening, pulmonary hyperinsufflation, atelectasis, and bronchiectasis).

Such clinical improvement must be interpreted with caution. It is known that the diameter of small airways is disproportionately smaller in infants, contributing to an increased proportion of total airway resistance.⁵⁰⁻⁵² As the child grows up, this proportion is gradually reduced,⁵⁰⁻⁵² and the small airways become more "silent" in terms of signs and symptoms.^{45,53} Therefore, the same degree of inflammatory lesion in the small airways may cause less intense respiratory signs and symptoms in older children than in infants. In this sense, the clinical improvement observed in patients with postinfectious BO may result from growth, and not necessarily from regression of bronchopulmonary lesions. The factors that could have influenced the clinical and radiological evolution of the 31 patients at Hospital de Clínicas de Porto Alegre were not clearly established, but being older at the moment of the first episode of acute viral bronchiolitis and an elevated serum IgE level seem to be unfavorable prognostic factors.

Finally, it is worth mentioning a clinical/radiological variation of postinfectious BO, Swyer-James syndrome, or Macleod syndrome.^{54,55} At the moment of diagnosis, these patients generally present few symptoms, except for a typical radiological image: hyperlucent lungs with normal or reduced volume.^{56,57}

Diagnosis and investigation: The diagnosis of postinfectious BO is based on clinical data.^{20-22,48} Usually, respiratory signs and symptoms of acute viral bronchiolitis disappear within 5 to 7 days,⁵⁸ but may last for 2 weeks in severe cases.⁵⁹ If the evolution does not occur as expected, and respiratory symptoms and signs persist, a diagnosis of postinfectious BO must be considered. For the differential diagnosis, diseases that may cause chronic airflow obstruction, such as gastroesophageal reflux, cystic fibrosis, pulmonary tuberculosis, immunodeficiency, and α -1-antitrypsin deficiency must be excluded on the basis of clinical, radiological, and laboratory investigation. Another disorder that may confuse the diagnosis of postinfectious

BO is postbronchiolitis recurrent wheeze, which may affect up to 75% of the patients with acute viral bronchiolitis.⁶⁰ The main differences between postbronchiolitis recurrent wheeze and postinfectious BO appear in Table 2.

The diagnostic investigation of BO includes thorax X-rays, pulmonary scintigraphy, high resolution computed tomography, and open pulmonary biopsy.^{9,20,48,61} Radiographic findings, such as bronchial thickening, pulmonary hyperinsufflation, atelectasis, and bronchiectasis, are not specific, but indicate that the lesions are restricted to the airways. The perfusion and ventilation lung scan shows the characteristic pattern of a matched ventilation-perfusion defect (Figure 4). Compared to thorax X-rays, pulmonary scintigraphy is more accurate in terms of defining the extension and location of bronchopulmonary lesions.⁶¹ Recently, high resolution computed tomography, considered the most adequate examination for assessment of lesions in the small airways, has been used in the investigation of patients with postinfectious BO.^{61,62} The main findings of high resolution computed tomography are bronchial thickening, bronchiectasis, atelectasis, and mixed areas of hypo/hyperattenuation (Figure 5). Hypo and hyperattenuation imaging, also called mosaic perfusion or mosaic pattern of pulmonary attenuation, is the most important sign of small airway lesions. Despite the superiority of high resolution computed tomography to define the nature, location, and extension of bronchopulmonary lesions, the high cost, excessive radiation dose, and technical complexity of this examination prevent its generalized use in the investigation of postinfectious BO. Open pulmonary biopsy, considered the gold standard, is generally not required for the diagnosis of postinfectious BO.^{20,48} This examination may be indicated for patients who present progressive deterioration even after treatment.^{20,22} Constrictive bronchiolitis is the main histopathological finding of postinfectious BO in children.²²

A defined protocol for the investigation of suspected postinfectious BO is not available. The flow chart presented is based on our own clinical experience (Figure 6).

Table 2 - Differential diagnosis: postbronchiolitis recurrent wheezing and postinfectious BO

Postinfectious	Postbronchiolitis BO	Recurrent wheeze
Symptomatology	Persistent	Recurrent
Fine crackles	Persistent	Absent
Radiological alterations	Persistent	Recurrent
Pathophysiology	Obliteration of bronchioles	Bronchial hyperresponsiveness
Response to bronchodilator use	Unsatisfactory	Satisfactory
Prognosis	Unfavorable	Favorable

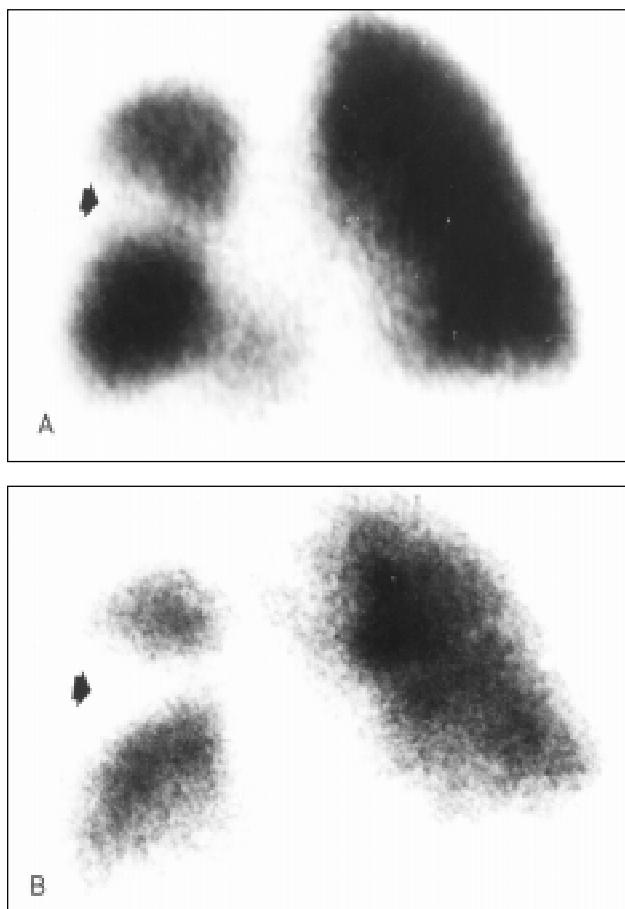


Figure 4 - Perfusion and ventilation lung scan, showing “matched defects” (arrows). **A** - Perfusion lung scan. **B** - Ventilation lung scan

Treatment: Due to the lack of an effective therapeutic method^{20,22,48} the basic treatment for postinfectious BO entails management of the disease. Concerning systemic corticotherapy, until the present moment, there are no clinical assays to evaluate its effect on patients with postinfectious BO. The use of corticosteroids is based on the work of Moran and Hellstron, who suggested that the early administration of this drug prevents the appearance of BO induced by intratracheal instillation of nitric acid in rabbits.⁶³ The therapeutic effect of corticosteroids in patients with BOOP has been clinically demonstrated.^{14,30,35,64} In addition, there are reports showing a significant effect of corticosteroids on patients with BO, suggested by the reduction of neutrophil level in the bronchoalveolar lavage fluid and by the improvement in pulmonary function.^{65,66} However, due to the lack of evidence concerning therapeutic effect, and to the high rate of side effects, systemic corticosteroids must be used with care in patients with postinfectious BO.

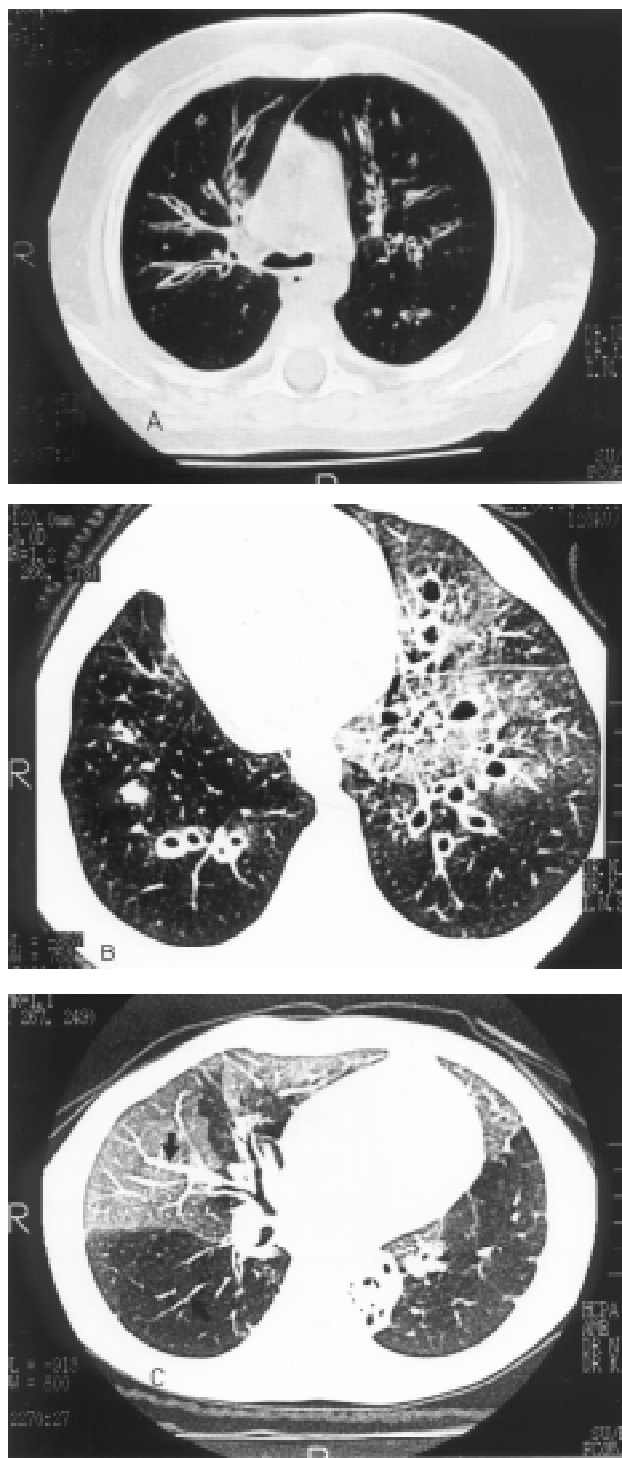


Figure 5 - Main findings of high-resolution computed tomography. **A** - An axial tomographic section shows mild cylindrical bronchiectasis with bronchial thickening on the upper right and left sides, longitudinally to the bronchium. **B** - Section showing mild cylindrical bronchiectasis with bronchial thickening in the lower left side and lingula thickening transversally to the bronchial axis. **C** - Tomographic section showing hypo and hyperattenuation areas in the LM, LID and lingula. Note that the caliber of the pulmonary vessels in the hyperattenuation area is higher than in the hypoattenuation area (arrow)

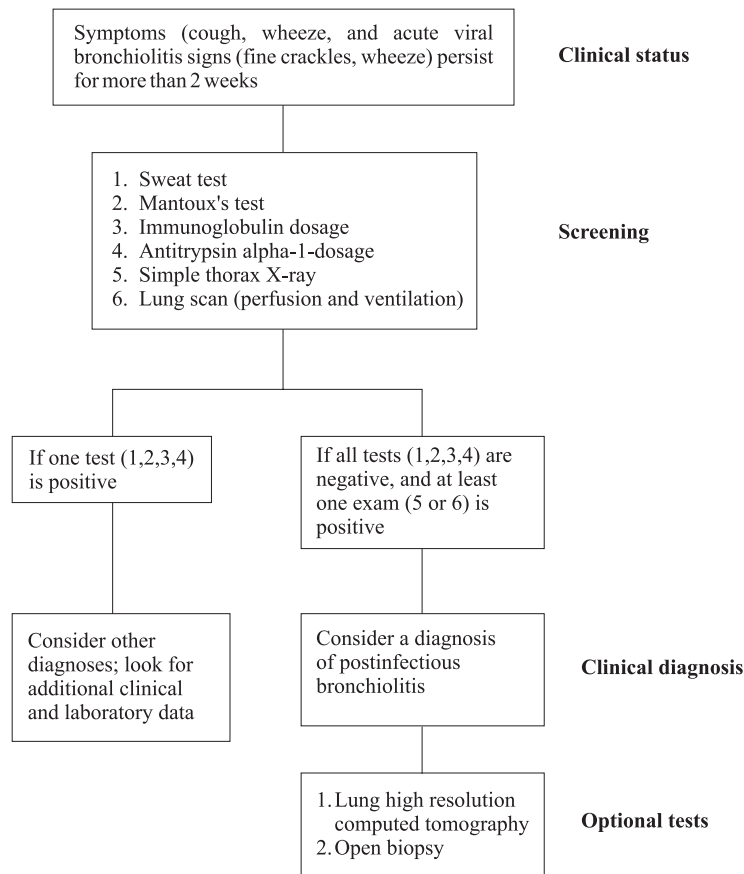


Figure 6 - Investigation of postinfectious BO

Bronchodilators are indicated in patients who present a response on pulmonary function tests and/or clinical assessment.⁴⁸ Generally, the response of patients with postinfectious BO to the use of bronchodilators is unpredictable.²²

Lung physiotherapy may be useful in patients with bronchiectasis, in whom mucociliary functions were impaired by the inflammatory alteration of the bronchial tree.⁴⁸ In these patients, antibiotic therapy is required in situations of clinical exacerbation, mainly during winter months.^{20,22} *Streptococcus pneumoniae* and *Haemophilus influenzae* are the main microorganisms identified in these patients, and, therefore, amoxicillin, ampicillin, chloramphenicol, and sulfamethoxazole-trimethoprim are the antibiotics of choice.²²

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