

Bronchiolitis

Brian T. Garibaldi, MD^a, Peter Illei, MD^b,
Sonye K. Danoff, MD, PhD^{c,*}

KEYWORDS

- Bronchiolitis • Constrictive bronchiolitis • Bronchiolitis obliterans
- Small airways obstruction

KEY POINTS

- Bronchiolitis is a disease of the small airways accompanied by progressive and often irreversible airflow obstruction.
- Bronchiolitis can be caused by several different processes including infectious, toxic exposure, collagen vascular disease, post lung and stem cell transplant, and idiopathic.
- Symptoms of chronic cough and sputum production are often mistaken for chronic obstructive pulmonary disease or asthma, leading to a delay in diagnosis.
- Mosaic perfusion and expiratory air trapping on high-resolution computed tomography are the hallmarks of bronchiolitis.
- Treatment of bronchiolitis depends in part on etiology, but is often ineffective.

INTRODUCTION

Bronchiolitis refers to inflammation occurring in the smaller conducting airways of the lung, typically in segments that are less than 2 mm in diameter.¹ Bronchiolitis was first reported in the literature by Wilhelm Lange in 1901 when he used the term “bronchiolitis obliterans” in an autopsy report of 2 patients who likely had what would now be described as cryptogenic organizing pneumonia (COP) (an entity formerly known as bronchiolitis obliterans organizing pneumonia [BOOP]).^{2,3} Soon thereafter Fraenkel described the pathology of bronchiolitis obliterans caused by inhalation of nitrogen oxide.^{3,4} Bronchiolitis is often a confusing entity because it may develop in isolation

Funding sources: Dr Garibaldi: None. Dr Illei: None. Dr Danoff: American College of Rheumatology Within Our Reach, Lisa Sandler Spaeth and Robert M. Fisher Funds for Pulmonary Fibrosis. Conflicts of interest: None.

^a Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA; ^b Department of Pathology, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, USA; ^c Division of Pulmonary and Critical Care Medicine, Johns Hopkins Interstitial Lung Disease Clinic, Johns Hopkins University School of Medicine, 1830 East Monument Street, Baltimore, MD 21205, USA

* Corresponding author.

E-mail address: sdanoff@jhmi.edu

Immunol Allergy Clin N Am 32 (2012) 601–619

<http://dx.doi.org/10.1016/j.iac.2012.08.002>

immunology.theclinics.com

0889-8561/12/\$ – see front matter © 2012 Elsevier Inc. All rights reserved.

or as a secondary feature of a diffuse lung disease. The number of potential causes of bronchiolitis, ranging from infectious etiology to environmental insults to autoimmune disease, further complicates the clinician’s approach to bronchiolitis.

Anatomy of Bronchioles

Bronchioles, in contrast to larger bronchi, do not have cartilage, glands, or goblet cells. Bronchioles are arranged in parallel, which maximizes cross-sectional area while minimizing their contribution to overall airflow resistance in the healthy lung.⁵ However, because of their relatively thin walls, bronchioles become narrowed at low lung volumes and their resistance increases as the lung approaches residual volume.⁶ In the context of inflammation or obstruction, their contribution to overall airflow resistance can become substantial and can lead to significant respiratory impairment.

Causes of Bronchiolitis

Bronchiolitis can be classified based on histopathologic or radiologic criteria, but it is perhaps most useful to think about bronchiolitis in terms of the likely clinical etiology (Box 1). In children younger than 2 years, bronchiolitis is the most frequently diagnosed respiratory disorder,⁷ with the vast majority of cases attributable to viral infection, particular respiratory syncytial virus (RSV), enteroviruses, and rhinoviruses.⁸ While less common in adults, infectious bronchiolitis can be the result of viral infections (adenovirus, influenza and parainfluenza, and so forth) as well as *Legionella pneumophila* and *Mycoplasma pneumonia*.^{9,10} Mycobacterial infections can also cause subacute and chronic bronchiolitis.¹¹ Common noninfectious causes of adult bronchiolitis include inhalational injury (including tobacco smoke), drug-induced, collagen vascular disease, post lung transplant, post bone marrow transplant, and idiopathic.¹² The term bronchiolitis obliterans (BO) is often used to describe these seemingly unrelated conditions in which the common finding is functional obstruction of bronchioles.¹³

CLINICAL PRESENTATION

The clinical presentation of bronchiolitis depends in part on the etiology. In children, infectious bronchiolitis is typically acute in onset and is associated with fever, cough, rhinorrhea, expiratory wheezing and, occasionally, frank respiratory distress.¹⁴ In older children and adults, isolated infectious bronchiolitis in the absence of bronchopneumonia is extremely rare, but may occur with *Mycoplasma pneumonia*. Such patients present with acute onset cough, dyspnea, fever, and even pleuritic chest pain.¹⁵

Box 1
Potential causes of bronchiolitis
Infectious
Postinfectious
Inhalational injury
Diffuse panbronchiolitis
Toxic ingestion
Collagen vascular disease associated
Post lung transplant
Post stem cell transplant
Idiopathic

In most cases of infectious bronchiolitis, the disease is self-limited and rarely lasts longer than 7 to 10 days.¹⁴

In the case of inhalational exposures, patients may present with acute symptoms related to airway injury or chemical pneumonitis, or they may have a delayed onset of cough and breathlessness weeks after the initial insult.¹⁶ In most other forms of adult bronchiolitis, patients present with a more subacute and slowly progressive course. Patients may complain of several weeks to months of worsening dyspnea and cough, often accompanied by signs and symptoms of air trapping and irreversible airflow obstruction. Patients may also have intermittent episodes of acute bronchiolitis accompanied by symptom worsening.¹ These symptoms are often attributed to underlying chronic obstructive pulmonary disease (COPD) or asthma, leading to a substantial delay in diagnosis.¹⁷

The presence of an underlying disease known to be associated with small airways disease (ie, post bone marrow transplant, post lung transplant, collagen vascular disease, and so forth) should prompt a search for bronchiolitis in patients with unexplained breathlessness, cough, or airflow obstruction. Patients with bronchiolitis may be asymptomatic in the early stages of disease, so screening with pulmonary function testing, imaging, and even bronchoscopy can identify high-risk patients before overt pulmonary symptoms develop.¹⁸

PHYSICAL EXAMINATION

The physical examination in patients with bronchiolitis is often nonspecific, but may suggest the presence of small airways disease including diffuse expiratory wheezing.¹⁹ Mid-inspiratory squeaks are present in 40% to 60% of patients.²⁰ Patients with advanced BO may have inspiratory crackles on auscultation.¹⁹ In patients with systemic disorders such as a collagen vascular disease, there may be findings associated with the systemic disorder on physical examination.

RADIOGRAPHIC FINDINGS

Radiographic findings in patients with bronchiolitis are often nonspecific but may provide clues to the presence of an underlying bronchiolar disorder. Bronchioles are not visible on standard chest radiographs, but obstruction of small airways may result in air trapping or hyperinflation. Sequential radiographs may show worsening hyperinflation in the absence of parenchymal disease.¹⁹ High-resolution computed tomography (HRCT) has revolutionized the contribution of imaging to the diagnostic workup of suspected bronchiolitis. Even though normal bronchioles are too small to be effectively imaged by HRCT, both direct and indirect signs of diseased bronchioles can be seen (**Table 1**).²¹

Direct Signs of Bronchiolitis

Thickening of bronchiolar walls by an inflammatory infiltrate or filling of the lumen or surrounding interstitium with an exudate will make the bronchial wall directly visible

Table 1
Radiographic signs of bronchiolitis

Direct Signs of Bronchiolitis	Indirect Signs of Bronchiolitis
Centrilobular thickening and peripheral nodules	Mosaic attenuation
Tree-in-bud opacities	Air trapping (accentuated on expiratory CT)
Bronchiolectasis	

on computed tomography (CT). Centrilobular thickening is the earliest sign of inflammation and may be seen as small peripheral nodules. Worsening bronchiolar inflammation associated with early mucoid impaction will create a “tree-in-bud” appearance visible as centrilobular branching structures that terminate in a nodule (**Fig. 1A**). The presence of tree-in-bud-opacities most often indicates an infectious bronchiolitis.²² Progressive inflammation and obstruction may lead to bronchiolar dilation (bronchiolectasis) identified as a cystic or tubular structure in the secondary pulmonary lobule (**Fig. 1B**).¹¹

Indirect Signs of Bronchiolitis

Indirect signs of bronchiolitis may be seen on standard HRCT performed at end-inspiration. Luminal obstruction of bronchioles will result in a segment of underventilated, and subsequently underperfused lung from compensatory hypoxic-pulmonary vasoconstriction. This process results in a patchy “mosaic attenuation pattern” whereby areas of bronchiolitis appear darker secondary to decreased perfusion (**Fig. 2**). The mosaic pattern is enhanced by obtaining images at end-expiration. Areas with luminal obstruction will not empty on expiration and will appear darker in comparison with unobstructed areas (**Fig. 3**).^{21,23,24} This “air trapping” is essentially the radiographic correlate to airflow obstruction seen on pulmonary function testing in patients with bronchiolitis. Findings of unilateral hypoattenuation and air trapping are suggestive of the Swyer-James and Macleod syndrome, which is likely the consequence of a postinfectious bronchiolitis.^{25,26} However, the isolated finding of air trapping on expiratory CT must be interpreted in the clinical context because healthy subjects, particularly smokers, can have expiratory air trapping on HRCT in the absence of overt clinical disease.²⁷

PULMONARY FUNCTION TESTING

Bronchiolitis is a disease of the small airways. As a result, the classic finding on pulmonary function testing is airflow obstruction on spirometry with or without evidence of air trapping or hyperinflation on lung volumes.^{12,28} In general, this airflow obstruction is less responsive to bronchodilators than are asthma or COPD, although the degree of reversibility varies depending on the underlying etiology. Diffusing capacity may be normal or reduced depending on the specific etiology and the presence or absence of associated bronchopneumonia or interstitial disease.¹⁹

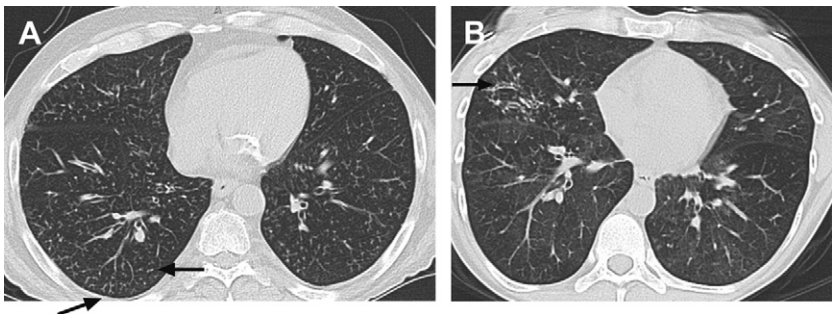


Fig. 1. (A) Computed tomography (CT) showing multiple small centrilobular nodules as well as tree-in-bud opacities (arrows) in an immunocompromised patient with disseminated aspergillosis. (B) CT showing bronchiolectasis (arrow) and bronchiectasis in a patient with common variable immune deficiency.



Fig. 2. CT showing mosaic perfusion in a patient with bronchiolitis associated with collagen vascular disease (arrows).

PATHOLOGIC FINDINGS

The pathologic findings in bronchiolitis depend in part on the underlying cause of the disorder. Several histopathologic classification systems have been developed, which has led to some degree of confusion regarding terminology. This section reviews the most commonly described types of bronchiolitis (**Table 2**).

Cellular Bronchiolitis

Cellular bronchiolitis refers to the presence of any inflammatory cells in the bronchiolar wall or lumen. It is commonly observed in infectious bronchiolitis as well as in association with asthma, chronic bronchitis, bronchiectasis, and hypersensitivity pneumonitis. There are 4 types of cellular bronchiolitis that deserve particular attention: follicular bronchiolitis, diffuse panbronchiolitis (DPB), lymphocytic bronchiolitis, and respiratory bronchiolitis.²³

Follicular bronchiolitis refers to the presence of lymphoid hyperplasia with secondary germinal centers along the bronchioles (**Fig. 4**).²² Centrilobular and peribronchial nodules are the radiographic correlate of this lymphoid hyperplasia.²⁹ Follicular bronchiolitis may result from immunodeficiency, hypersensitivity reactions, and collagen vascular disease (especially rheumatoid arthritis and Sjögren syndrome), and as a distal reaction in the setting of bronchiectasis of any cause.²³

DPB is a type of bronchiolitis most commonly seen in East Asian men. It is characterized histopathologically by chronic inflammation and the accumulation of foamy macrophages in the walls of respiratory bronchioles.³⁰

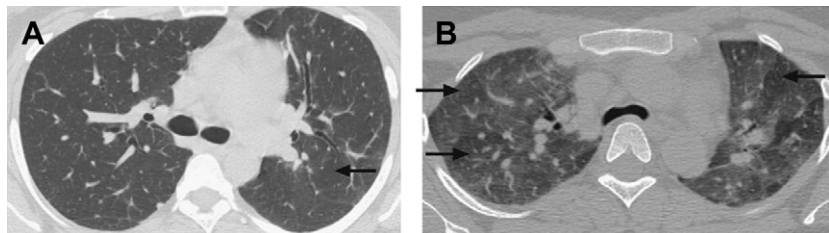


Fig. 3. (A) Inspiratory CT showing subtle areas of mosaic perfusion (arrow) in a patient with bronchiolitis. (B) Expiratory CT in same patient showing multiple areas of hypoattenuation consistent with air trapping (arrows). The bowing forward of the cartilaginous component of the trachea confirms that this is an expiratory CT. (Courtesy of David Feigin, MD, Department of Radiology, Johns Hopkins University School of Medicine.)

Table 2 Pathologic classification of bronchiolitis		
Classification	Pathologic Features	Clinical Associations
Cellular bronchiolitis		
Follicular bronchiolitis	Lymphoid hyperplasia with secondary germinal centers	Collagen vascular disease (especially rheumatoid arthritis and Sjögren), immunodeficiency, hypersensitivity, lymphoproliferative disease, diffuse panbronchiolitis
Diffuse panbronchiolitis	Chronic inflammation with foamy macrophages in bronchiole walls	Clinical syndrome in East Asia, often associated with chronic sinusitis
Lymphocytic bronchiolitis	Lymphocyte infiltration in bronchiole walls	Rejection post lung transplant, infection, in association with lymphocytic interstitial pneumonia
Respiratory bronchiolitis	Pigmented macrophages in bronchiole lumen	Tobacco smoking in isolation or with associated interstitial lung disease
Proliferative bronchiolitis	Intraluminal buds of fibrotic tissue	Commonly occurs with organizing pneumonia (ie, cryptogenic organizing pneumonia)
Constrictive bronchiolitis	Concentric narrowing or obliteration of bronchiole lumen by submucosal and peribronchiolar fibrosis	Idiopathic, postinfectious, collagen vascular disease, inhalational or toxic exposure, post lung transplant, post stem cell transplant

Lymphocytic bronchiolitis is characterized by the presence of lymphocyte infiltration in the walls of the respiratory bronchioles. It can be seen in several infectious and inflammatory states, but is most commonly associated with acute allograft rejection in lung transplantation (**Fig. 5**).³¹

Respiratory bronchiolitis is characterized by the presence of pigmented macrophages in the bronchiolar lumen. It is most often an incidental finding in smokers, but may be associated with a mild form of interstitial lung disease called respiratory bronchiolitis–interstitial lung disease (RB-ILD) (**Fig. 6**).³²

Proliferative Bronchiolitis

Proliferative bronchiolitis is characterized by intraluminal buds of fibrotic tissue (or Masson bodies) in the respiratory bronchioles (**Fig. 7**). Proliferative bronchiolitis may occur in isolation, but is most often associated with an organizing pneumonia that extends into the alveolar ducts and alveoli.^{13,33,34} This bronchiolitis obliterans with organizing pneumonia was historically called BOOP, but has recently been reclassified as cryptogenic organizing pneumonia (COP). This change in nomenclature underscores the fact that the features of organizing pneumonia, and not airflow obstruction, dominate the clinical picture.²³ A more detailed description of COP is provided elsewhere in this issue.

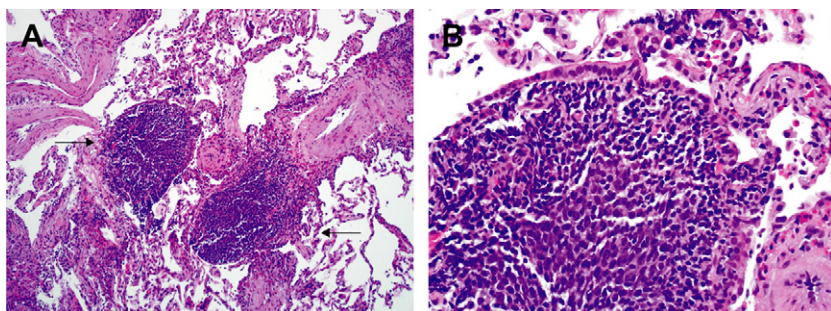


Fig. 4. Follicular bronchiolitis in a patient with bronchiectasis secondary to chronic *Mycobacterium avium-intracellulare* infection. (A) Low-power view demonstrates the presence of lymphoid hyperplasia with secondary germinal centers (arrows) (hematoxylin and eosin, original magnification $\times 100$). (B) Higher-power view of germinal center showing dense lymphoid aggregates (hematoxylin and eosin, original magnification $\times 400$).

Constrictive Bronchiolitis

Constrictive bronchiolitis is characterized by narrowing and eventual obliteration of respiratory bronchioles by peribronchiolar and submucosal fibrosis (**Fig. 8**).²³ The term BO used to describe the clinical syndrome of irreversible airflow obstruction most often refers to constrictive bronchiolitis. Constrictive bronchiolitis can be the consequence of several different insults including inhalational injury, infection, collagen vascular disease, and post lung transplant and stem cell transplant.¹⁴ Several of these causes are discussed in more detail in the following section.

BRONCHIOLITIS TREATMENT

Bronchiolitis is a challenging airway disorder to treat. The airflow obstruction in bronchiolitis is usually not responsive to bronchodilator therapy.¹⁹ Corticosteroids and other immunomodulating therapies have been used in several bronchiolar diseases, often with little or no response, although they may be effective in certain subtypes

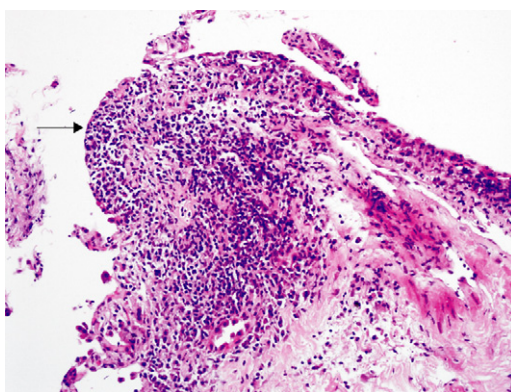


Fig. 5. Lymphocytic bronchiolitis in a lung transplant patient. This transbronchial biopsy shows a bronchiole with dense lymphocytic transmural infiltrate (arrow). The infiltrate is seen in all layers of the respiratory mucosa and in surrounding soft tissue, and includes scattered plasma cells and mononuclear cells (hematoxylin and eosin, magnification $\times 200$).

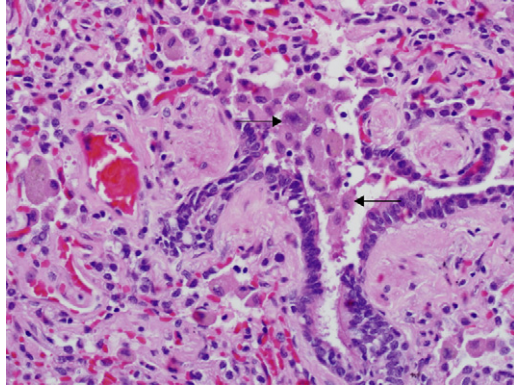


Fig. 6. Respiratory bronchiolitis in an active tobacco smoker. This high-magnification ($\times 400$) view of a bronchiole shows a cluster of dusky pigmented macrophages in the lumen (*arrows*) and thickening of the basement membrane. The surrounding alveoli are also filled with similar dusky pigmented macrophages. No significant interstitial fibrosis or remodeling is present (Hematoxylin and eosin).

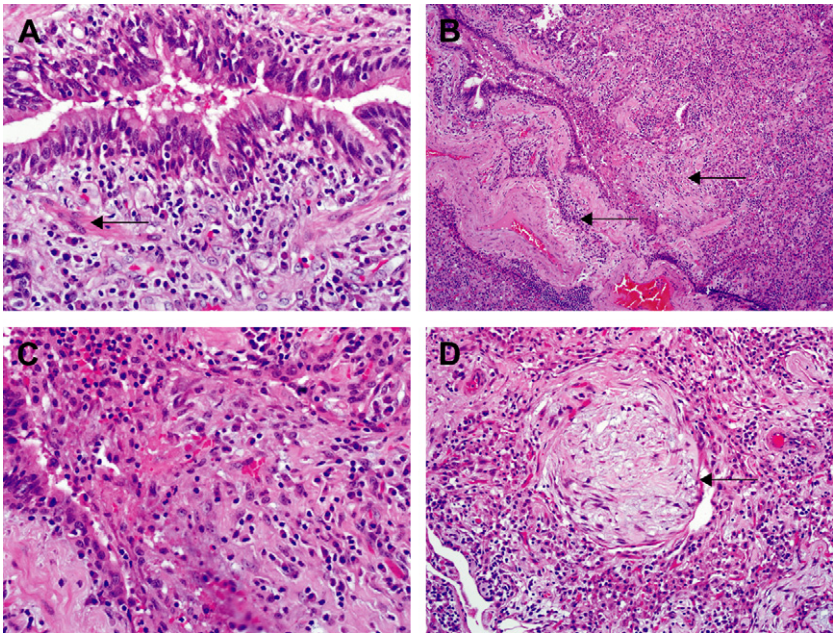


Fig. 7. Proliferative bronchiolitis with organizing pneumonia in a patient with suspected collagen vascular disease. (A) The bronchioles show variable chronic subepithelial inflammation with associated proliferation of fibroblasts (*arrow*) (Hematoxylin and eosin, magnification $\times 400$). (B) Some airways demonstrate intraluminal buds of granulation tissue with associated inflammation (*arrows*) (Hematoxylin and eosin, magnification $\times 100$). (C) Higher-power view of airway intraluminal buds (Hematoxylin and eosin, magnification $\times 400$). (D) The surrounding parenchyma shows organization with numerous intra-alveolar fibroblast plugs filling the lumina (*arrow*) (Hematoxylin and eosin, magnification $\times 400$).

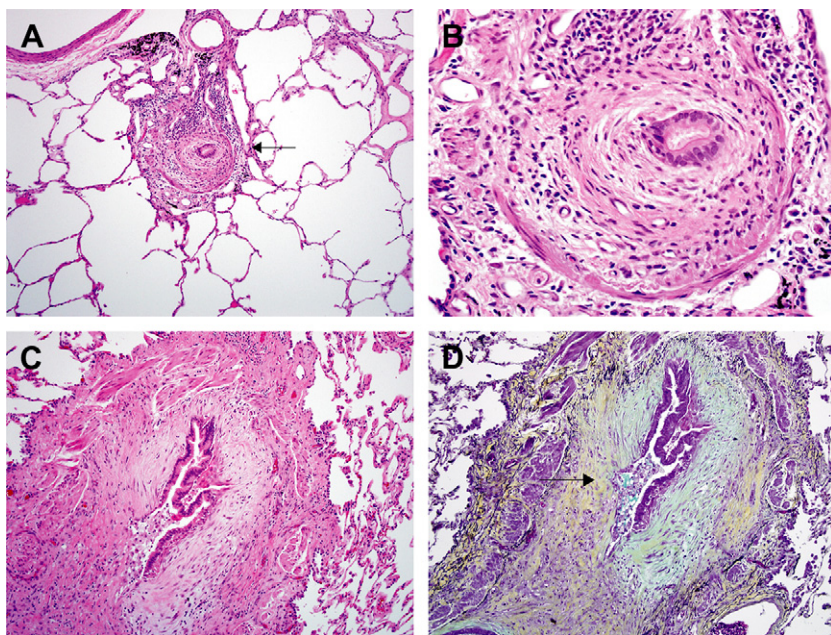


Fig. 8. Constrictive bronchiolitis. (A) Lung biopsy in a previously healthy 56-year-old woman showing scattered small airways with concentric subepithelial fibrosis and marked narrowing of the lumen (arrow) (Hematoxylin and eosin, magnification $\times 100$). (B) Higher-power view demonstrating marked bronchiolar narrowing and fibrosis (Hematoxylin and eosin, magnification $\times 400$). (C) Lung biopsy from a stem cell transplant patient showing marked subepithelial fibrosis (Hematoxylin and eosin, magnification $\times 400$). (D) Movat stain from the same biopsy highlighting the subepithelial fibrosis (arrow).

of bronchiolitis. Specific therapies are discussed next, in the context of the bronchiolitis subtypes.

SPECIFIC CAUSES OF BRONCHIOLITIS

There are several conditions associated with the development of bronchiolitis. Although the pathologic presence of isolated bronchiolitis is by itself nonspecific, the finding of bronchiolitis should prompt an evaluation for an associated or known cause.¹ Some of the more commonly encountered causes of bronchiolitis are reviewed here.

Postinfectious

As already described, acute infection is an extremely common cause of bronchiolitis in children and can also occur in adults. Although this acute bronchiolitis is usually self-limited, a small number of both pediatric and adult patients will develop a progressive BO.^{35,36} Postinfectious bronchiolitis in children is frequently caused by adenovirus infection.³⁷ Histopathology may reveal an initial proliferative bronchiolitis followed by a later constrictive pattern, depending on the timing of the biopsy.^{12,38} Patients ultimately recover, although long-term sequelae such as the Swyer-James and Macleod syndrome may develop, characterized by regional airflow obstruction, often in a unilateral distribution.^{12,25,26,35}

Treatment of postinfectious bronchiolitis includes both inhaled and systemic corticosteroids in an attempt to reduce inflammation, short-acting and long-acting bronchodilators for wheezing, antibiotics for recurrent infection from poor airway clearance, and supplemental oxygen as needed.³⁷ Some clinicians advocate the use of azithromycin based on its apparent benefit in other forms of bronchiolitis, although its efficacy in this context is unknown.³⁹ In rare cases, lung transplantation may be indicated in the setting of progressive respiratory failure.¹²

Inhalational Injury

The inhalation of a variety of different gases, fumes, dusts, or organic substances may lead to significant airway injury (Table 3).²³ Following an acute exposure, patients may experience severe symptoms including laryngospasm, bronchiolar spasm, reflex respiratory arrest, or asphyxia. Death may occur following a massive exposure. If patients inhale the substance deeply enough into the lungs, acute pulmonary edema can develop from a chemical pneumonitis. Following the initial exposure, patients will uncommonly develop 1 of 2 syndromes: (1) prolonged reactive airways disease, termed the reactive airway dysfunction syndrome (RADS); or (2) constrictive bronchiolitis.^{12,33,40}

The most commonly recognized cause of bronchiolitis after inhalational exposure is nitrogen dioxide. Nitrogen dioxide can reach the periphery of the lung, where it forms both nitric and nitrous acids as well as nitrous oxide. If inhaled in high enough concentrations, patients may develop acute or delayed (3–30 hours later) pulmonary edema and Acute Respiratory Distress Syndrome.^{12,41} After recovery, or in asymptomatic patients, symptoms of cough and progressive dyspnea may develop 2 to 6 weeks after the initial exposure, accompanied by progressive and usually irreversible airflow obstruction.^{42,43} The airflow obstruction correlates with a progressive constrictive bronchiolitis seen on histopathology.^{13,23}

The first death from acute inhalation of nitrogen dioxide was reported by Desgranges in 1804 when he described the case of a man who died of respiratory failure after a bottle of nitric acid broke and reacted with a woodpile.^{41,44} Fraenkel was the first to report histopathologic BO in association with nitrogen gas exposure.⁴ Today, inhalational injury from nitrogen dioxide is commonly referred to as silo filler’s disease because nitrogen dioxide and dinitrogen tetroxide are found in the air on the surface of silage in agricultural silos.^{12,43}

Table 3 Exposures that may result in bronchiolitis	
Toxic Inhalation/Ingestion	Potential Source
Nitrogen dioxide	Grain silos
Sulfur	Chemical warfare (ie, mustard gas)
Diacetyl	Artificial butter flavoring in microwave popcorn
Chlorine	Household or industrial bleach; chemical warfare
Phosgene	Pesticides and plastics manufacturing; chemical warfare
Flock	Synthetic fabric manufacturing
Mineral dust	Asbestos, aluminum, silica, iron oxide, coal
Gastric contents	Acute large-volume aspiration; chronic aspiration
Penicillamine	Treatment of collagen vascular disease
Gold	Treatment of rheumatoid arthritis
<i>Sauropus androgynus</i>	Raw vegetable used in Asia for weight loss

Several other gases and volatile compounds have been reported in association with the development of BO. Perhaps the best known is the development of BO in several employees at a microwave popcorn factory, thought to be secondary to exposure to diacetyl, a ketone used as an artificial butter flavoring.^{17,45} Constrictive bronchiolitis has recently been described in soldiers returning from Iraq and Afghanistan. In some of these cases, exposure to a sulfur-mine fire may have been the direct cause.⁴⁶ Survivors of the World Trade Center bombing on September 11, 2001, as well as other terrorist attacks, have been reported to have features of BO following massive dust particle exposure.⁴⁷

A history of known exposure to a potentially toxic irritant should be sought in all patients with a suspected or confirmed diagnosis of bronchiolitis. Patients who present following an acute inhalational exposure should be observed for at least 48 hours in the hospital and then followed expectantly for the development of BO in the weeks to months following the index event.¹² If acute respiratory symptoms develop, clinical experience with nitrogen dioxide injury suggests that corticosteroids may improve symptoms and prevent disease progression.^{16,42,48} Relapse of BO after removal of steroids has been described, prompting some clinicians to advocate at least a 2-month course of treatment.¹² Removal of the inciting toxic agent is critical and in some cases may result in complete recovery. For example, BO secondary to nylon fibers in synthetic fabrics (ie, flock worker's lung) may improve substantially after the exposure is removed.⁴⁹ BO from diacetyl inhalation does not appear to resolve after removal of the exposure, but lung function will generally not worsen.¹⁷

Drug-Induced

Whereas COP has been reported as a potential adverse reaction to several different medications, isolated BO associated with pharmacologic treatments is rare. Isolated BO has been reported after gold therapy and penicillamine treatment in patients with rheumatoid arthritis (RA). It is difficult to determine if the therapy or the disease process was the cause because BO has been described in RA patients in the absence of these therapies.^{50,51} BO has also been reported after rituximab therapy in a patient with B-cell lymphoma.⁵² Over-the-counter and herbal therapies have been associated with the development of BO. For example, ingestion of uncooked *Sauropus androgynus*, a vegetable with supposed weight-loss properties, led to an outbreak of BO in young women in both Taiwan and Japan.^{53,54} Even though drug-induced BO is rare, a thorough exposure history, including over-the-counter and herbal remedies, should be obtained from any patient presenting with unexplained bronchiolitis. Corticosteroids may play some role in the treatment of drug-induced BO in the setting of collagen vascular disease, but were of limited benefit in BO caused by *S androgynus*.⁵³

Diffuse Panbronchiolitis

DPB is a distinct form of bronchiolitis that is found almost exclusively in East Asia. It was first recognized in Japan in the 1960s⁵⁵ and has since been seen in both Korea and China. Rare cases have been reported outside of Asia.⁵⁶ This may in part be explained by a close association of DPB with HLA Bw54, which is predominantly found in Asian populations.⁵⁷ The incidence of DPB was as high as 11.1 per 100,000 in Japan in 1980, but may have decreased in recent years.⁵⁸ Mean age at presentation is 50 years, with a 2:1 male/female predominance. Most patients have a history of long-standing chronic sinusitis before they develop pulmonary manifestations. Symptoms include chronic cough and copious purulent sputum production, in some cases up to 50 mL per day.^{58,59} Pulmonary function testing reveals marked obstruction that is not responsive to bronchodilators. Chest radiographs may reveal

bilateral nodular infiltrates, particularly in a lower lobe distribution. HRCT will characteristically show centrilobular nodules and may also show a tree-in-bud pattern. Bronchiectasis is often present in advanced disease.^{11,58} Patients with DPB often have marked elevation in serum cold agglutinins with negative *Mycoplasma pneumonia* antibody titers, suggesting that this is in response to chronic inflammation and not acute *Mycoplasma* infection.¹² The most distinctive feature on biopsy is chronic inflammation accompanied by the presence of foam cells in the walls of respiratory bronchioles.^{1,30} If untreated, 50% of patients with DPB die within 5 years of diagnosis, in part because of secondary bacterial infections associated with bronchiectasis and poor airway clearance.

In the 1980s, physicians in Japan realized that patients with DPB who were treated with erythromycin appeared to do better over the long term. Subsequent studies revealed that survival in patients on low-dose erythromycin increased from 63% to 91%.⁶⁰ Since then, these observations have been extended to include other macrolides such as clarithromycin and azithromycin.⁶¹ The effectiveness of macrolide therapy is not thought to be secondary to its antibacterial properties, because patients with *Pseudomonas* infection also improve with therapy. Several mechanisms have been postulated to play a role including decreased neutrophil recruitment, reduction in mucus production, decreased lymphocyte accumulation, and modulation of bacterial virulence.^{58,61} These observations have led to the use of macrolides in other forms of bronchiolitis.

Collagen Vascular Disease–Associated Bronchiolitis

Bronchiolitis has been described in association with several connective tissue diseases. In fact, in nontransplant-related cases of BO, connective tissue disease has been estimated to account for 25% to 50% of reported cases.^{20,62} The incidence of isolated bronchiolitis appears to be highest in patients with RA and Sjögren syndrome, although cases have been reported in patients with systemic lupus erythematosus, scleroderma, and even inflammatory bowel disease (Table 4).^{20,63,64}

Rheumatoid arthritis

Perhaps the best-known association between collagen vascular disease and bronchiolar disorders occurs in patients with RA. Although several pulmonary complications can be seen in patients with RA, it has been estimated that up to 68% of asymptomatic patients with RA have evidence of bronchiolar disease on HRCT imaging.^{20,65} Pulmonary function testing in RA patients with normal HRCT scans suggests that an additional 30% of asymptomatic patients have some degree of airflow obstruction.⁶⁶ In patients who develop severe, symptomatic airflow obstruction (defined as forced expiratory volume in 1 second/forced vital capacity less than 50% or residual volume/total lung capacity greater than 140% predicted), the predominant histologic

Table 4 Collagen vascular diseases commonly associated with bronchiolar involvement	
Collagen Vascular Disease	Bronchiolar Complications
Rheumatoid arthritis	Follicular bronchiolitis, constrictive bronchiolitis, bronchiectasis, cryptogenic organizing pneumonia (COP)
Sjögren syndrome	Lymphocytic bronchiolitis, constrictive bronchiolitis (usually in secondary Sjögren syndrome), rare COP
Systemic lupus erythematosus	COP, rare constrictive bronchiolitis
Inflammatory bowel disease	Lymphocytic bronchiolitis

pattern is usually constrictive bronchiolitis, although some patients may also have features of follicular bronchiolitis.⁶⁷ Patients with constrictive bronchiolitis will have characteristic mosaic perfusion and expiratory air trapping on HRCT. Follicular bronchiolitis may produce centrilobular and peribronchial nodules.⁶⁸ Up to 40% of patients will also have evidence of coexisting bronchiectasis on HRCT. Patients with significant airflow obstruction will complain of dyspnea on exertion and almost half will have bronchorrhea. Almost all patients with symptomatic bronchiolar disease have a preexisting diagnosis of RA at the time of symptom onset.⁶⁷ Prognosis in these patients is poor, with progression to respiratory failure within 3 to 4 years of diagnosis.^{33,67} RA patients with secondary Sjögren syndrome may be at increased risk for developing BO.^{20,69} As mentioned previously, treatment of RA with both gold and penicillamine has been associated with a higher risk of developing BO, although the role of these drugs in such development is controversial.^{50,51}

Several agents have been used to treat BO in RA patients, with limited success. Corticosteroids with the addition of either azathioprine or cyclophosphamide have been reported to cause a transient improvement but have not resulted in long-term remission.^{20,70} Erythromycin has been used to treat both follicular bronchiolitis and BO in patients with RA. In one small case series, 11 of 15 patients symptomatically improved and none died over a 2-year follow-up period.⁷¹

Sjögren syndrome

Sjögren syndrome may occur as an isolated disease or as a secondary phenomenon in patients with another connective tissue disease, most commonly RA and SLE. The prevalence of symptomatic airflow obstruction in association with bronchiolitis is not well described. Air trapping is present on pulmonary function testing in as many as half of patients with primary Sjögren syndrome.^{20,72} HRCT may reveal bronchial wall thickening, bronchiectasis, bronchiolectasis, tree-in-bud opacities, and air trapping. Sjögren patients can develop lymphocytic bronchiolitis with or without coexisting lymphocytic interstitial pneumonia (LIP). In both cases, lymphocytic infiltration into the walls of the small bronchioles leads to obstruction, which can present as small nodules and even cystic structures on HRCT.⁶⁸ Constrictive bronchiolitis has been described in patients with RA and secondary Sjögren syndrome, but is not commonly seen as an isolated lesion in primary Sjögren syndrome.²⁸

The optimal treatment of bronchiolitis in patients with Sjögren syndrome is unknown. In cases of lymphocytic bronchiolitis associated with LIP, corticosteroids are generally used, as about half of patients with "idiopathic" LIP will improve on corticosteroids.⁷³ Similarly, if follicular bronchiolitis is seen in conjunction with either LIP or nonspecific interstitial pneumonia (NSIP), treatment is directed at the associated interstitial lung disease. Corticosteroids appear to be beneficial in follicular bronchiolitis, and progression to respiratory failure is rare.⁷⁴

Post Lung Transplant

Post lung transplant bronchiolitis obliterans syndrome (BOS) is the most common cause of BO and continues to be one of the most important factors limiting survival in lung transplant recipients. BOS is the clinical manifestation of chronic allograft rejection and is defined by progressive airflow obstruction in the absence of acute rejection, infection, or other known cause.⁷⁵ In patients who survive to 5 years after transplant, more than 50% will develop BOS.⁷⁶ The onset of BOS confers a 5-year mortality of 50% to 70%.^{18,77} Patients who present earlier after transplant or with severe disease have increased mortality.⁷⁸ On histopathology BOS usually manifests as a constrictive bronchiolitis, but may have features of a proliferative bronchiolitis.¹⁹ Several

mechanisms are thought to play a role in the development of BOS including T-cell activation, circulating antibodies, innate immune responses to environmental insults (ie, infection), and even autoimmunity directed against type 5 collagen.⁷⁹ BOS is closely associated with episodes of acute rejection (AR) and is seen at a higher frequency in patients who have had multiple episodes of AR.⁸⁰ Lymphocytic bronchiolitis, either in isolation or as part of AR, appears to be of particular importance in causing epithelial injury and downstream fibroproliferation, and has been shown to be highly associated with the development of BOS.^{31,75} Few therapies improve outcomes in patients once BOS has developed, and despite advances in the early detection and treatment of acute rejection, the prevalence of BOS has not appreciably changed in recent years.⁷⁹

Changing the primary immunosuppressive regimen (ie, converting cyclosporine to tacrolimus or azathioprine to mycophenolate mofetil) has been shown in small studies to stabilize the course of BOS.^{81,82} Extracorporeal photopheresis (ECP) and total lymphoid irradiation (TLI) have been shown to slow the decline in lung function in patients with BOS, although the side effects of TLI may be poorly tolerated.^{83–86} Several small studies have shown that low-dose azithromycin 3 times per week may slow or even reverse the decline in lung function from BOS.⁸⁵ Azithromycin may prevent the development of chronic rejection and BOS in some patients,⁸⁷ although recent data regarding the risk of sudden cardiac death after treatment of bacterial infections with azithromycin may temper its routine use in all transplant patients.⁸⁸

Post Bone Marrow Transplant

Patients who undergo allogeneic stem cell transplantation (SCT) are at risk of developing a BOS that is similar in clinical presentation and pathology to post lung transplantation BOS. It is likely that both syndromes represent an alloimmune response: host versus graft in the case of lung transplant, and graft versus host in the case of SCT.⁸⁹ BOS was first reported as a complication of graft-versus-host disease (GVHD) in 1982.⁹⁰ It has since been recognized as the most common and significant pulmonary manifestation of GVHD, and is included in the National Institutes of Health consensus criteria for diagnosing chronic GVHD.⁹¹ The prevalence of BOS after SCT has been reported to be as high as 5.5% in all SCT patients and up to 14% in patients with chronic GVHD.⁹² It usually occurs within the first 2 years post transplant but has been reported up to 5 years after SCT. Patients usually lack respiratory symptoms during the initial phases of BOS but may manifest other signs of chronic GVHD such as liver, skin, and eye involvement.⁹³ As BOS progresses patients experience dyspnea on exertion and a persistent nonproductive cough, similar to other forms of BO.⁹⁴

Despite effective therapies for other tissue complications of chronic GVHD, long-term outcomes for patients with SCT-related BOS are dismal; survival is 20% at 2 years and only 13% at 5 years.^{93,95–97} Patients who present more than 1 year after SCT may have a slightly improved survival. Most centers monitor SCT patients with routine pulmonary function testing to detect the presence of asymptomatic small airways disease in the hope that identification of patients at risk for BOS will allow for earlier treatment that might halt airway obliteration.^{93,98} Once BOS is recognized, several therapies have been used based on the lung transplant experience. No therapy has been rigorously studied in the SCT population.^{89,93}

Corticosteroids remain the mainstay of treatment with or without the addition of calcineurin inhibitors, rapamycin, and mycophenolate mofetil. Azithromycin has been used with mixed results in small case series.^{89,99} ECP and TLI have also been used, with limited success.⁸⁹ Recently, pulmonary rehabilitation has been shown to improve 6-minute walk distance, dyspnea, and exercise tolerance in SCT patients with BOS, and may be an important adjunctive therapy.¹⁰⁰

SUMMARY

Bronchiolitis can result from several infectious, inflammatory, and environmental insults. It is often a confusing clinical entity because of overlapping terminology and the existence of several histopathologic, radiographic, and clinical classification systems. Patients may present with chronic cough and dyspnea and are often thought to have asthma or COPD, leading to a delay in diagnosis. Chest radiography may be unremarkable but high-resolution CT often reveals mosaic perfusion and expiratory air trapping. Treatment and long-term prognosis are determined in part by the underlying etiology, although many types of bronchiolitis are poorly responsive to therapy. Post lung transplant and stem cell transplant bronchiolitis are the most frequently encountered, and provide important insights into the immune pathogenesis and treatment of this diverse group of disorders.

REFERENCES

1. Visscher DW, Myers JL. Bronchiolitis. *Proc Am Thorac Soc* 2006;3:41–7.
2. Lange W. Ueber eine eigenthümliche Erkrankung der kleinen Bronchien und Bronchiolen. *Dtsch Arch Klin Med* 1901;70:342–64.
3. Poletti V, Costabel U. Bronchiolar disorders: classification and diagnostic approach. *Semin Respir Crit Care Med* 2003;24(5):457–64.
4. Fraenkel A. Ueber Bronchiolitis fibrosa obliterans, nebst Bemerkungen über Lungenhyperaemie und indurierende Pneumonie. *Dtsch Arch Klin Med* 1902;73:484–510.
5. Albertine KH. Anatomy of the lungs. In: Mason RD, Broaddus VC, Martin TR, et al, editors. *Murray and Nadel's textbook of respiratory medicine*. 5th edition. Philadelphia: Elsevier; 2010. p. 3–25.
6. Hughes JM, Rosenzweig DY, Kivitz PB. Site of airway closure in excised dog lungs: histologic demonstration. *J Appl Phys* 1970;29:340–4.
7. Flaherman V, Ragins A, Li S, et al. Frequency, duration and predictors of bronchiolitis episodes of care among infants [greater than or equal to] 32 weeks gestation in a large integrated healthcare system: a retrospective cohort study. *BMC Health Serv Res* 2012;12:144.
8. Huguenin A, Moutte L, Renois F, et al. Broad respiratory virus detection in infants hospitalized for bronchiolitis by use of a multiplex RT-PCR DNA microarray system. *J Med Virol* 2012;84:979–85.
9. Cha SI, Shin KM, Kim M, et al. *Mycoplasma pneumoniae* bronchiolitis in adults: clinicoradiologic features and clinical course. *Scand J Infect Dis* 2009;41:515–9.
10. Andersen P. Pathogenesis of lower respiratory tract infections due to Chlamydia, Mycoplasma, Legionella and viruses. *Thorax* 1998;53:302–7.
11. Lynch DA. Imaging of small airways disease and chronic obstructive pulmonary disease. *Clin Chest Med* 2008;29(1):165–79.
12. King TE. Miscellaneous causes of bronchiolitis: inhalational, infectious, drug-induced, and idiopathic. *Semin Respir Crit Care Med* 2003;24(5):567–76.
13. Epler GR, Colby TV. The spectrum of bronchiolitis obliterans. *Chest* 1983;83(2):161–2.
14. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics* 2006;118:1774–93.
15. Chan ED, Kalayanamit T, Lynch DA, et al. *Mycoplasma pneumoniae*-associated bronchiolitis causing severe restrictive lung disease in adults: report of three cases and literature review. *Chest* 1999;115:1188–94.

16. Milne JE. Nitrogen dioxide inhalation and bronchiolitis obliterans. A review of the literature and report of a case. *J Occup Med* 1969;11(10):538–47.
17. van Rooy FG, Rooyackers JM, Prokop M, et al. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med* 2007;176:498–504.
18. Belperio JA, Lake K, Tazelaar H, et al. Bronchiolitis obliterans syndrome complicating lung or heart-lung transplantation. *Semin Respir Crit Care Med* 2003;24(5):499–530.
19. Angel L, Homma A, Levine SM. Bronchiolitis obliterans. *Semin Respir Crit Care Med* 2000;21(2):123–34.
20. White E, Tazelaar HD, Lynch JP. Bronchiolar complications of connective tissue diseases. *Semin Respir Crit Care Med* 2003;24(5):543–66.
21. Hansell DM. HRCT of obliterative bronchiolitis and other small airways diseases. *Semin Roentgenol* 2001;36:51–65.
22. Devakonda A, Raoof S, Sung A, et al. bronchiolar disorders: a clinical-radiological diagnostic algorithm. *Chest* 2010;137:938–51.
23. Kang E, Woo OH, Shin BK, et al. Bronchiolitis: classification, computed tomographic and histopathologic features, and radiologic approach. *J Comput Assist Tomogr* 2009;33(1):32–41.
24. Jensen SP, Lynch DA, Brown KK, et al. High-resolution CT features of severe asthma and bronchiolitis obliterans. *Clin Radiol* 2002;57:1078–85.
25. Swyer P, James G. Case of unilateral pulmonary emphysema. *Thorax* 1953;8:133–6.
26. Macleod WM. Abnormal translucency of one lung. *Thorax* 1954;9:147–53.
27. Lee KW, Chung SY, Yang I, et al. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects¹. *Radiology* 2000;214:831–6.
28. Turton CW, Williams G, Green M. Cryptogenic obliterative bronchiolitis in adults. *Thorax* 1981;36(11):805–10.
29. Howling SJ, Hansell DM, Wells AU, et al. Follicular bronchiolitis: thin-section CT and histologic findings. *Radiology* 1999;212:637–42.
30. Iwata M, Colby TV, Kitaichi M. Diffuse panbronchiolitis: diagnosis and distinction from various pulmonary diseases with centrilobular interstitial foam cell accumulations. *Hum Pathol* 1994;25:357–63.
31. Girgis RE, Berry GJ, Reichenspurner H, et al. Risk factors for the development of obliterative bronchiolitis after lung transplantation. *J Heart Lung Transplant* 1996;15:1200–8.
32. Wright JL, Tazelaar HD, Churg A. Fibrosis with emphysema. *Histopathology* 2011;58:517–24.
33. Epler GR. Bronchiolar disorders with airflow obstruction. *Curr Opin Pulm Med* 1996;2(2):134–40.
34. Epler GR, Colby TV, McLoud TC, et al. Bronchiolitis obliterans organizing pneumonia. *N Engl J Med* 1985;312:152–8.
35. Kurland G, Michelson P. Bronchiolitis obliterans in children. *Pediatr Pulmonol* 2005;39:193–208.
36. Wright JL. Diseases of the small airways. *Lung* 2002;176(6):375–96.
37. Fischer GB, Sarria EE, Mattiello R, et al. Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev* 2010;11:233–9.
38. Mauad T, Dolhnikoff M. Histology of childhood bronchiolitis obliterans. *Pediatr Pulmonol* 2002;33:466–74.
39. De Baets F. Bronchiolitis obliterans in children: a ghostly journey to the origin. *Allergol Immunopathol* 2011;39:251–2.

40. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376–84.
41. Smith DL. Criteria for a recommended standard: occupational exposures to oxides of nitrogen (nitrogen dioxide and nitric oxide). Washington, DC: National Institute for Occupational Safety and Health; 1976. p. 76–149.
42. Fleming GM, Chester EH, Montenegro HD. Dysfunction of small airways following pulmonary injury due to nitrogen dioxide. *Chest* 1979;75(6):720–1.
43. Gurney JW, Unger JM, Dorby CA, et al. Agricultural disorders of the lung. *Radiographics* 1991;11:625–34.
44. Desgranges JB. Observation and comments on a sudden death caused by nitrous gas. *J Med Chir Pharm* 1804;8:487–505.
45. Kreiss K, Gomaa A, Kullman G, et al. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med* 2002;347:330–8.
46. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med* 2011;365:222–30.
47. Ghanei M, Harandi AA, Tazelaar HD. Isolated bronchiolitis obliterans: high incidence and diagnosis following terrorist attacks. *Inhal Toxicol* 2012;24:340–1.
48. Horvath EP, doPico GA, Barbee RA, et al. Nitrogen dioxide-induced pulmonary disease: five new cases and a review of the literature. *J Occup Med* 1978;20(2): 103–10.
49. Kern DG, Kuhn C III, Ely EW, et al. Flock worker's lung—broadening the spectrum of clinicopathology, narrowing the spectrum of suspected etiologies. *Chest* 2000;117:251–9.
50. Tomioka R, King TE. Gold-induced pulmonary disease: clinical features, outcome, and differentiation from rheumatoid lung disease. *Am J Respir Crit Care Med* 1997;155:1011–20.
51. Turner-Warnick M. Adverse reactions affecting the lung: possible association with D-penicillamine. *J Rheumatol Suppl* 1981;7:166–8.
52. Shen T, Braude S. Obliterative bronchiolitis after rituximab administration: a new manifestation of rituximab-associated pulmonary toxicity. *Intern Med J* 2012;42: 597–9.
53. Lai RS, Chiang AA, Wu MT, et al. Outbreak of bronchiolitis obliterans associated with consumption of *Sauropus androgynus* in Taiwan. *Lancet* 1996;348:83–5.
54. Oonakahara K, Matsuyama W, Higashimoto J, et al. Outbreak of bronchiolitis obliterans associated with consumption of *Sauropus androgynus* in Japan—alert of food-associated pulmonary disorders from Japan. *Respiration* 2005; 72:221.
55. Homma H, Yamanaka A, Tanimoto S, et al. Diffuse panbronchiolitis. A disease of the transitional zone of the lung. *Chest* 1983;83:63–9.
56. Fitzgerald JE, King TE, Lynch DA, et al. Diffuse panbronchiolitis in the United States. *Am J Respir Crit Care Med* 1996;154:497–503.
57. Sugiyama Y, Kudoh S, Maeda H, et al. Analysis of HLA antigens in patients with diffuse panbronchiolitis. *Am J Respir Crit Care Med* 1990;141:1459–62.
58. Kudoh S, Keicho N. Diffuse panbronchiolitis. *Clin Chest Med* 2012;33:297–305.
59. Homma H. Diffuse panbronchiolitis. *Jpn J Med* 1986;25:329–34.
60. Kudoh S, Azuma A, Yamamoto M, et al. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998;157:1829–32.
61. Li H, Zhou Y, Fan F, et al. Effect of azithromycin on patients with diffuse panbronchiolitis: retrospective study of 51 cases. *Intern Med* 2011;50:1663–9.

62. Katzenstein AL, Myers JL, Prophet WD, et al. Bronchiolitis obliterans and usual interstitial pneumonia. A comparative clinicopathologic study. *Am J Surg Pathol* 1986;10(6):373–81.
63. Yousem SA. The pulmonary manifestations of the CREST syndrome. *Hum Pathol* 1990;21(5):467–74.
64. Camus P, Piard F, Ashcroft T, et al. The lung in inflammatory bowel disease. Baltimore (MD): Medicine; 1993. 151–183.
65. Demir R, Bodur H, Tokoglu F, et al. High resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Rheumatol Int* 1999;19:19–22.
66. Mori S, Koga Y, Sugimoto M. Small airway obstruction in patients with rheumatoid arthritis. *Mod Rheumatol* 2011;21:164–73.
67. Devouassoux G, Cottin V, Lioté H, et al. Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. *Eur Respir J* 2009;33:1053–61.
68. Lynch DA. Lung disease related to collagen vascular disease. *J Thorac Imaging* 2009;24:299–309.
69. Bégin R, Massé S, Cantin A, et al. Airway disease in a subset of nonsmoking rheumatoid patients: characterization of the disease and evidence for an autoimmune pathogenesis. *Am J Med* 1982;72:743–50.
70. Wells AU, du Bois RM. Bronchiolitis in association with connective tissue disorders. *Clin Chest Med* 1993;14:655–66.
71. Hayakawa H, Sato A, Imokawa S, et al. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med* 1996;154:1531–6.
72. Lahdensuo A, Korpela M. Pulmonary findings in patients with primary Sjögren's syndrome. *Chest* 1995;108:316–9.
73. Cha SI, Fessler MB, Cool CD, et al. Lymphoid interstitial pneumonia: clinical features, associations and prognosis. *Eur Respir J* 2006;28:364–9.
74. Aerni MR, Vassallo R, Myers JL, et al. Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients. *Respir Med* 2008;102:307–12.
75. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002;21:297–310.
76. Christie JD, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. *J Heart Lung Transplant* 2010;29:1104–18.
77. Valentine VG, Robbins RC, Berry GJ, et al. Actuarial survival of heart-lung and bilateral sequential lung transplant recipients with obliterative bronchiolitis. *J Heart Lung Transplant* 1996;15:371–83.
78. Finlen Copeland CA, Snyder LD, Zaas DW, et al. Survival after bronchiolitis obliterans syndrome among bilateral lung transplant recipients. *Am J Respir Crit Care Med* 2010;182:784–9.
79. Todd JL, Palmer SM. Bronchiolitis obliterans syndrome in lung transplantation: the final frontier for lung transplantation. *Chest* 2011;140:502–8.
80. Husain AN, Siddiqui MT, Holmes EW, et al. Analysis of risk factors for the development of bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 1999;159:829–33.
81. Whyte RI, Rossi SJ, Mulligan MS, et al. Mycophenolate mofetil for obliterative bronchiolitis syndrome after lung transplantation. *Ann Thorac Surg* 1997;64:945–8.
82. Cairn J, Yek T, Banner NR, et al. Time-related changes in pulmonary function after conversion to tacrolimus in bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2003;22:50–7.

83. Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010;29:424–31.
84. Benden C, Speich R, Hofbauer GF, et al. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. *Transplantation* 2008;86:1625–7.
85. Hayes D. A review of bronchiolitis obliterans syndrome and therapeutic strategies. *J Cardiovasc Surg* 2011;6:92.
86. Verleden GM, Lievens Y, Dupont LJ, et al. Efficacy of total lymphoid irradiation in azithromycin nonresponsive chronic allograft rejection after lung transplantation. *Transplant Proc* 2009;41:1816–20.
87. Vos R, Vanaudenaerde BM, Ottevaere A, et al. Long-term azithromycin therapy for bronchiolitis obliterans syndrome: divide and conquer? *J Heart Lung Transplant* 2010;29:1358–68.
88. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881–90.
89. Sengsayadeth SM, Srivastava S, Jagasia M, et al. Time to explore preventive and novel therapies for bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2012. [Epub ahead of print].
90. Roca J, Granena A, Rodriguez-Roisin R, et al. Fatal airway disease in an adult with chronic graft-versus-host disease. *Thorax* 1982;37:77–8.
91. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005;11:945–56.
92. Au BK, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2011;17:1072–8.
93. Williams KM, Chien JW, Gladwin MT, et al. Bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *JAMA* 2009;302:306–14.
94. Clark JG, Crawford SW, Madtes DK, et al. Obstructive lung disease after allogeneic marrow transplantation. *Ann Intern Med* 1989;111:368.
95. Chien JW, Martin PJ, Gooley TA, et al. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2003;168:208–14.
96. Chan CK, Hyland RH, Hutcheon MA, et al. Small-airways disease in recipients of allogeneic bone marrow transplants. An analysis of 11 cases and a review of the literature. *Medicine (Baltimore)* 1987;66:327–40.
97. Dudek AZ, Mahaseth H, DeFor TE, et al. Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. *Biol Blood Marrow Transplant* 2003;9:657–66.
98. Forsl w U, Mattsson J, Gustafsson T, et al. Donor lymphocyte infusion may reduce the incidence of bronchiolitis obliterans after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2011;17:1214–21.
99. Lam DC, Lam B, Wong MK, et al. Effects of azithromycin in bronchiolitis obliterans syndrome after hematopoietic SCT—a randomized double-blinded placebo-controlled study. *Bone Marrow Transplant* 2011;46:1551–6.
100. Tran J, Norder EE, Diaz PT, et al. Pulmonary rehabilitation for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2012;18(8):1250–4.