Bronchiolitis

Brian T. Garibaldi, MD\textsuperscript{a}, Peter Illei, MD\textsuperscript{b}, Sonye K. Danoff, MD, PhD\textsuperscript{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.\textsuperscript{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]).\textsuperscript{2,3} Soon thereafter Fraenkel described the pathology of bronchiolitis obliterans caused by inhalation of nitrogen oxide.\textsuperscript{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.
\textsuperscript{a} Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA; \textsuperscript{b} Department of Pathology, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, USA; \textsuperscript{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
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. However, because of their relatively thin walls, bronchioles become narrowed at low lung volumes and their resistance increases as the lung approaches residual volume. 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, with the vast majority of cases attributable to viral infection, particular respiratory syncytial virus (RSV), enteroviruses, and rhinoviruses. 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*. Mycobacterial infections can also cause subacute and chronic bronchiolitis. 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. The term bronchiolitis obliterans (BO) is often used to describe these seemingly unrelated conditions in which the common finding is functional obstruction of bronchioles.

**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. 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.

<table>
<thead>
<tr>
<th>Box 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential causes of bronchiolitis</strong></td>
</tr>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>Postinfectious</td>
</tr>
<tr>
<td>Inhalational injury</td>
</tr>
<tr>
<td>Diffuse panbronchiolitis</td>
</tr>
<tr>
<td>Toxic ingestion</td>
</tr>
<tr>
<td>Collagen vascular disease associated</td>
</tr>
<tr>
<td>Post lung transplant</td>
</tr>
<tr>
<td>Post stem cell transplant</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>
In most cases of infectious bronchiolitis, the disease is self-limited and rarely lasts longer than 7 to 10 days. 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. 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. These symptoms are often attributed to underlying chronic obstructive pulmonary disease (COPD) or asthma, leading to a substantial delay in diagnosis.

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.

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. Mid-inspiratory squeaks are present in 40% to 60% of patients. Patients with advanced BO may have inspiratory crackles on auscultation. 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. 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.

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>
<thead>
<tr>
<th>Direct Signs of Bronchiolitis</th>
<th>Indirect Signs of Bronchiolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrilobular thickening and peripheral nodules</td>
<td>Mosaic attenuation</td>
</tr>
<tr>
<td>Tree-in-bud opacities</td>
<td>Air trapping (accentuated on expiratory CT)</td>
</tr>
<tr>
<td>Bronchiolectasis</td>
<td></td>
</tr>
</tbody>
</table>
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. Progressive inflammation and obstruction may lead to bronchiolar dilatation (bronchiolectasis) identified as a cystic or tubular structure in the secondary pulmonary lobe (Fig. 1B).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
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.

Follicular bronchiolitis refers to the presence of lymphoid hyperplasia with secondary germinal centers along the bronchioles (Fig. 4). Centrilobular and peribronchial nodules are the radiographic correlate of this lymphoid hyperplasia. 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.

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.

![Fig. 2.](image1) CT showing mosaic perfusion in a patient with bronchiolitis associated with collagen vascular disease (arrows).

![Fig. 3.](image2) (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.)
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 (Fig. 5).31

Respiratory bronchiolitis is characterized by the presence of pigmented macrophages in the bronchiole 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.

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

Constrictive bronchiolitis is characterized by narrowing and eventual obliteration of respiratory bronchioles by peribronchiolar and submucosal fibrosis (Fig. 8). 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. 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. 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. 6. Respiratory bronchiolitis in an active tobacco smoker. This high-magnification (×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 ×400). (B) Some airways demonstrate intraluminal buds of granulation tissue with associated inflammation (arrows) (Hematoxylin and eosin, magnification ×100). (C) Higher-power view of airway intraluminal buds (Hematoxylin and eosin, magnification ×400). (D) The surrounding parenchyma shows organization with numerous intra-alveolar fibroblast plugs filling the lumina (arrow) (Hematoxylin and eosin, magnification ×400).
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.\(^{12,25,26,36}\)
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. 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. In rare cases, lung transplantation may be indicated in the setting of progressive respiratory failure.

Inhalational Injury

The inhalation of a variety of different gases, fumes, dusts, or organic substances may lead to significant airway injury (Table 3). 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.

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. 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. The airflow obstruction correlates with a progressive constrictive bronchiolitis seen on histopathology.

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. Fraenkel was the first to report histopathologic BO in association with nitrogen gas exposure. 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.

<table>
<thead>
<tr>
<th>Exposures that may result in bronchiolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxic Inhalation/Ingestion</strong></td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>Sulfur</td>
</tr>
<tr>
<td>Diacetyl</td>
</tr>
<tr>
<td>Chlorine</td>
</tr>
<tr>
<td>Phosgene</td>
</tr>
<tr>
<td>Flock</td>
</tr>
<tr>
<td>Mineral dust</td>
</tr>
<tr>
<td>Gastric contents</td>
</tr>
<tr>
<td>Penicillamine</td>
</tr>
<tr>
<td>Gold</td>
</tr>
<tr>
<td>Sauropus androgynus</td>
</tr>
</tbody>
</table>
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. 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. 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.

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. If acute respiratory symptoms develop, clinical experience with nitrogen dioxide injury suggests that corticosteroids may improve symptoms and prevent disease progression. Relapse of BO after removal of steroids has been described, prompting some clinicians to advocate at least a 2-month course of treatment. 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. BO from diacetyl inhalation does not appear to resolve after removal of the exposure, but lung function will generally not worsen.

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. BO has also been reported after rituximab therapy in a patient with B-cell lymphoma. 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. 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 Sauropus androgynus.

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 1960s and has since been seen in both Korea and China. Rare cases have been reported outside of Asia. This may in part be explained by a close association of DPB with HLA Bw54, which is predominantly found in Asian populations. The incidence of DPB was as high as 11.1 per 100,000 in Japan in 1980, but may have decreased in recent years. 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. 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.\textsuperscript{11,58} Patients with DPB often have marked elevation in serum cold agglutinins with negative \textit{Mycoplasma pneumonia} antibody titers, suggesting that this is in response to chronic inflammation and not acute \textit{Mycoplasma} infection.\textsuperscript{12} The most distinctive feature on biopsy is chronic inflammation accompanied by the presence of foam cells in the walls of respiratory bronchioles.\textsuperscript{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%.\textsuperscript{60} Since then, these observations have been extended to include other macrolides such as clarithromycin and azithromycin.\textsuperscript{61} The effectiveness of macrolide therapy is not thought to be secondary to its antibacterial properties, because patients with \textit{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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>
<thead>
<tr>
<th>Collagen Vascular Disease</th>
<th>Bronchiolar Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Follicular bronchiolitis, constrictive bronchiolitis, bronchiectasis, cryptogenic organizing pneumonia (COP)</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Lymphocytic bronchiolitis, constrictive bronchiolitis (usually in secondary Sjögren syndrome), rare COP</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>COP, rare constrictive bronchiolitis</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Lymphocytic bronchiolitis</td>
</tr>
</tbody>
</table>

Garibaldi et al
pattern is usually constrictive bronchiolitis, although some patients may also have features of follicular bronchiolitis. Patients with constrictive bronchiolitis will have characteristic mosaic perfusion and expiratory air trapping on HRCT. Follicular bronchiolitis may produce centrilobular and peribronchial nodules. 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. Prognosis in these patients is poor, with progression to respiratory failure within 3 to 4 years of diagnosis. RA patients with secondary Sjögren syndrome may be at increased risk for developing BO. 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.

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. 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.

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. 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. 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.

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. 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.

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. In patients who survive to 5 years after transplant, more than 50% will develop BOS. The onset of BOS confers a 5-year mortality of 50% to 70%. Patients who present earlier after transplant or with severe disease have increased mortality. On histopathology BOS usually manifests as a constrictive bronchiolitis, but may have features of a proliferative bronchiolitis.
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. 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. 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. 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.

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. 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. 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. Azithromycin may prevent the development of chronic rejection and BOS in some patients, 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.

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. 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. 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. Azithromycin may prevent the development of chronic rejection and BOS in some patients, 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.

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. 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. 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. Azithromycin may prevent the development of chronic rejection and BOS in some patients, 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.

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. BOS was first reported as a complication of graft-versus-host disease (GVHD) in 1982. 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. 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. 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. As BOS progresses patients experience dyspnea on exertion and a persistent nonproductive cough, similar to other forms of BO.

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. 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. 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.

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. ECP and TLI have also been used, with limited success. 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.
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


