# EXPERT REVIEWS

# Bronchiolitis: adopting a unifying definition and a comprehensive etiological classification

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Bronchiolitis is an inflammatory and potentially fibrosing condition affecting mainly the intralobular conducting and transitional small airways. Secondary bronchiolitis participates in disease process of the airways and/or the surrounding lobular structures in the setting of several already defined clinical entities, mostly of known etiology, and occurs commonly. Primary or idiopathic bronchiolitis dominates and characterizes distinct clinical entities, all of unknown etiology, and occurs rarely. Secondary bronchiolitis regards infections, hypersensitivity disorders, the whole spectrum of smoking-related disorders, toxic fumes and gas inhalation, chronic aspiration, particle inhalation, drug-induced bronchiolar toxicities, sarcoidosis and neoplasms. Idiopathic or primary bronchiolitis defines clinicopathologic entities sufficiently different to be designated as separate disease entities and include cryptogenic constrictive bronchiolitis, diffuse panbronchiolitis, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, neuroendocrine hyperplasia in infants, bronchiolitis obliterans syndrome in lung and allogeneic hematopoietic cell transplantation, connective tissue disorders, inflammatory bowel disease and bronchiolitis obliterans organizing pneumonia. Most of the above are pathological descriptions used as clinical diagnosis. Acute bronchiolitis, though potentially life threatening, usually regresses. Any etiology chronic bronchiolitis contributes to morbidity and/or mortality if it persists and/or progresses to diffuse airway narrowing and distortion or complete obliteration. Bronchiolitis in specific settings leads to bronchiolectasis, resulting in bronchiectasis.

Bronchiolitis is an inflammatory and potentially fibrosing condition affecting mainly the intralobular conducting and transitional small airways. Secondary bronchiolitis participates in the disease process affecting the airways and/or the surrounding lobular structures in the setting of several already defined clinical entities, mostly of known etiology, and occurs commonly. Primary or idiopathic bronchiolitis dominates and characterizes distinct clinical entities, all of unknown etiology, and occurs rarely (Box 1 & Figure 1) [1–4]. Although international consensus guidelines on bronchiolar disorders are lacking, this review comprises a unifying definition of all-cause bronchiolitis, and since imaging and histopathological features overlap among several of the above conditions,

a comprehensive etiological classification is advanced.

Secondary bronchiolitis is common in: almost all causes of pulmonary infections [5]; hypersensitivity disorders such as bronchial asthma [6], allergic bronchopulmonary aspergillosis (ABPA) [7], bronchocentric granulomatosis [8], hypersensitivity pneumonia [9], chronic eosinophilic pneumonia (CEP) [10], eosinophilic granulomatosis and polyangiitis (Churg–Strauss syndrome) [11]; the whole spectrum of smoking-related disorders such as respiratory bronchiolitis (RB) in smokers and in chronic obstructive pulmonary disease (COPD) [12], RB-interstitial lung disease (RB-ILD) [13] and pulmonary Langerhans cells histiocytosis (PLCH) [14]; toxic fumes and gases inhalation [15]; diffuse chronic aspiration [16];

## Box 1. Bronchiolitis: a comprehensive etiological classification.

**Secondary**
- Infections
- Hypersensitivity disorders:
  – Bronchial asthma
  – Allergic bronchopulmonary aspergillosis
  – Bronchocentric granulomatosis
  – Hypersensitivity pneumonitis
  – Chronic eosinophilic pneumonia
  – Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
- Smoking-related disorders:
  – Smokers respiratory bronchiolitis and bronchiolitis in chronic obstructive pulmonary disease
  – Respiratory bronchiolitis interstitial lung disease
  – Pulmonary Langerhans cell histiocytosis
- Toxic fumes and gases inhalation
- Diffuse chronic aspiration
- Inhaled particle-induced small airways disease
- Drug-induced bronchiolar toxicities
- Sarcoidosis
- Neoplasms

**Idiopathic/primary**
- Cryptogenic constrictive bronchiolitis
- Diffuse panbronchiolitis
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- Neuroendocrine hyperplasia in infants
- Bronchiolitis obliterans syndrome
- Connective tissue disorders:
  – Primary Sjögren's syndrome
  – Rheumatoid arthritis
  – Systemic lupus erythematosus
  – Polymyositis–dermatomyositis
  – Mixed connective tissue disease
  – Ankylosing spondylitis
- Inflammatory bowel disease
- Bronchiolitis obliterans organizing pneumonia – cryptogenic organizing pneumonia

inhaled particle-induced small airways disease [17]; drug-induced bronchiolar toxicities [201]; sarcoidosis [18] and neoplasms. Most of the above conditions relate to well-defined etiological factors (**Box 2**).

Idiopathic or primary bronchiolitis defines clinicopathologic entities sufficiently different to be designated as separate disease entities in: cryptogenic constrictive bronchiolitis [19]; diffuse panbronchiolitis [20]; diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) [21] and neuroendocrine hyperplasia in infants (NEHI) [22]; bronchiolitis obliterans syndrome (BOS) in lung and allogeneic hematopoietic cell transplantation [23]; connective tissue disorders [24]; inflammatory bowel disease [25] and bronchiolitis obliterans organizing pneumonia (BOOP)–cryptogenic organizing pneumonia (COP) [26]. Most of the above are pathological descriptions that are used in clinical diagnosis, and all are idiopathic, nonrelated to identifiable etiological factors.

The spectrum of clinical manifestations in bronchiolitis depends on the clinical context of the myriad of clinical entities that may accompany, and extends from the total absence of symptoms in some conditions to dyspnea more or less rapidly progressing in the more severe cases. 'Sicca'/unproductive or productive cough with various qualities of sputum commonly coexists, the latter especially if bronchiolectasis–bronchiectasis ensue. Pulmonary function tests (PFTs), high-resolution computerized tomography (HRCT) and, in several cases, surgical lung biopsy are necessary to obtain diagnosis. Prognosis is variable (**Figure 2**). Acute bronchiolitis, though potentially life threatening, usually regresses. Any etiology chronic bronchiolitis contributes to morbidity if it persists and/or progresses to cause diffuse airway narrowing and distortion or complete obliteration – that is, constrictive–obliterans bronchiolitis – and may lead to respiratory failure and even death. Bronchiolitis in specific settings may lead to bronchiolectasis and mucus stasis, causing diffuse or localized bronchiectasis. Management strategies depend on the specific clinical setting.

### Anatomy of the secondary pulmonary lobule & histology of the bronchiole

The most important subsegmental lung units are the secondary pulmonary lobule and the lung acinus (**Figure 3**). The secondary pulmonary lobule, as defined by Miller, refers to the smallest unit of lung structure marginated by connective tissue septa that has a polyhedral shape measuring from 1 to 2.5 cm in diameter [27]. The pulmonary acinus is defined as the lung unit distal to a terminal bronchiole, which is the last purely conducting airway; thus, the acinus is the largest lung unit in which all airways participate in gas exchange [28]. Acini measure 6–10 mm in diameter. Secondary pulmonary lobules are made up of three to 24 acini. The secondary lobule is important, pathologically, because disease processes are intrenched by the connective tissue septa marginating the lobules. The alveolar ducts, alveolar sacs and alveoli distal to the last respiratory bronchiole make up the primary pulmonary lobule [27].

The pulmonary artery and bronchiolar branches supplying the lobule, lymphatics and supporting connective tissue, lie in the center of the secondary pulmonary lobule [28]. The arteries and bronchioles that supply the secondary lobules have a diameter of approximately 1 mm, the intralobular terminal bronchioles and arteries have a diameter of 0.7 mm, whereas the diameter of the acinar bronchioles and arteries measure from 0.3 to 0.5 mm. These arteries can be seen in HRCT but the visibility of bronchioles depends on their wall thickness [28].

The secondary pulmonary lobule is marginated by the connective tissue interlobular septa, which is part of the peripheral interstitial fiber system that extends inward from the pleural surface, and contains pulmonary veins and lymphatics [28]. These septa are at the lower limit of HRCT resolution.

The substance of the secondary lobule consists of alveoli and the associated pulmonary capillaries supplied by the bronchioles and branches of the pulmonary arteries, veins and lymphatics [29].
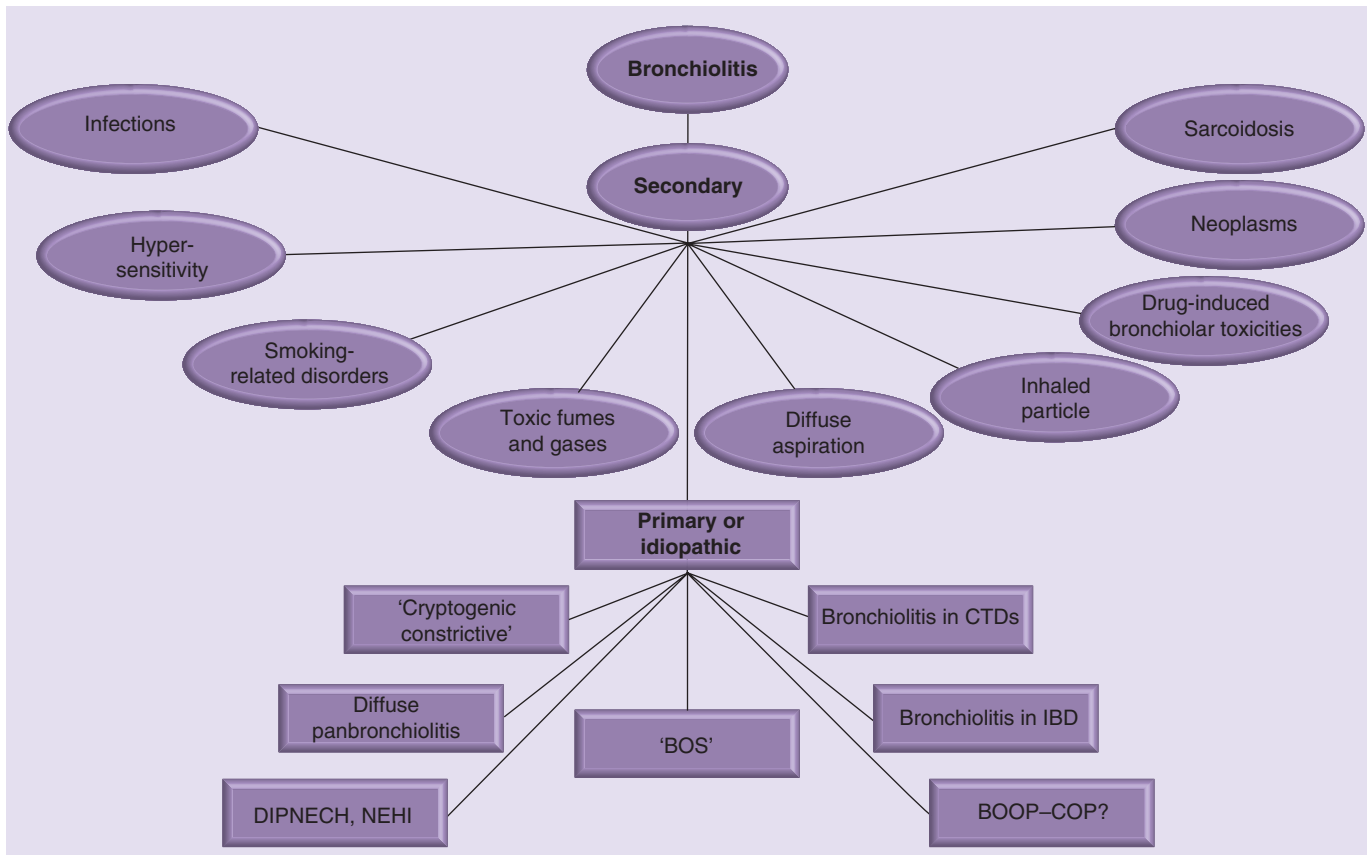
**Figure 1. Classification of bronchiolitis.** Secondary bronchiolitis participates in disease process affecting the airways and/or the surrounding lobular structures in the setting of several already defined clinical entities, mostly of known etiology, and occurs commonly. Idiopathic or primary bronchiolitis define clinicopathologic entities sufficiently different to be designated as separate disease entities, where predominates, and occurs rarely.
BOOP: Bronchiolitis obliterans organizing pneumonia; BOS: Bronchiolitis obliterans syndrome; COP: Cryptogenic organizing pneumonia; CTD: Connective tissue disorder; DIPNECH: Diffuse idiopathic pulmonary neuroendocrine cells hyperplasia; IBD: Inflammatory bowel disease; NEHI: Neuroendocrine hyperplasia in infants.

This parenchyma is supported by a fine network of very thin connective tissue fibers within the alveolar septa termed the 'septal fibers' or intralobular interstitium [29].

Bronchioles are the segments of the conductive portion of the airways that, in contrast to the bronchi, lack cartilage and submucosal glands. Bronchioles consist of three layers: the epithelium, the lamina propria and the submucosa. The epithelium is pseudostratified and columnar with scarce goblet and basal cells in the larger bronchioles and becomes cuboidal and ciliated with Clara cells in the smaller bronchioles [29]. Rarer cells in the bronchiolar epithelium are the neuroendocrine cells forming the neuroendocrine bodies and the brush cells [29]. The lamina propria is a thin layer of loose elastin-rich connective tissue with no glands right beneath the basement membrane. The submucosa consists of smooth muscle cells spiraling around the bronchioles and is surrounded by adventitia.

## Histopathology

Pathologists' classification of bronchiolitis is based mainly on descriptive microscopic morphology and includes acute/chronic or acute on chronic bronchiolitis, proliferative/obliterative patterns, granulomatous, cellular eosinophilic, neutrophilic or lymphocytic infiltrating patterns, follicular bronchiolitis, vanishing airways disease and a few others (**Figure 4A–G**) [30]. This relates to the fact that small airways respond to injury in a limited fashion of patterns. As a consequence, many of the above secondary but also idiopathic bronchiolitis processes (**Figure 1**) present overlapping histological features. Mostly in idiopathic bronchiolitis, the naming of the disease reflects pathological descriptions, which have become used as clinical diagnosis. In these cases, exclusion of secondary causes is imperative. Furthermore, very few specific microscopic morphological patterns, such as neuroendocrine hyperplasia and respiratory panbronchiolitis, become the appellative of specific clinical disorders as in DIPNECH, NEHI and diffuse panbronchiolitis. In this review, a unifying definition and a comprehensive etiological classification is presented. It needs to be noted that it is always important to correlate biopsy findings, when feasible, with clinical and imaging data to ensure an accurate diagnosis. In every chapter, a specific effort is undertaken in order to describe histopathology features of bronchiolar involvement in specific disorders.

## Box 2. Inhaled particles, toxic fumes and gases causing inhalation bronchiolitis.

**Inhaled particles**
- Asbestos
- Coal
- Sheet silicates
- Aluminum oxide
- Iron oxide
- Silica
- Ambient particulate air pollutants

**Toxic fumes and gases**
- Sulfur dioxide
- Chlorine gas
- Ammonia
- Nitrogen dioxide
- Phosgene
- Photochemical air pollutants
- Ozone
- Diacetyl

## Imaging in bronchiolitis

Chest radiographic findings of bronchiolitis are commonly non-specific, subtle or even totally lacking. If present, signs include various degrees of hyperinflation that may or may not be associated with signs of bronchiectasis (tram lines in bronchi seen longitudinally and when bronchial cuff is dilated bronchi are seen end-on) [31]. In HRCT, protocols with thin collimation (below 1 mm) and contiguous reconstructions allow accurate coronal or sagittal multiplanar reformats [32]. Expiratory HRCT may help in small airway assessment when seeking for air trapping [33]. Imaging features of bronchiolitis in HRCT can be divided into the following categories that, to a certain extent, correlate also with pathology: those in which wall thickening and luminal filling predominate, those in which an inflammatory process of the bronchiolar walls and adjacent alveoli coexist at various combinations, and those in which stenosis of the bronchioles predominates giving rise to manifestations related to various degrees of obstruction and hypoxic vasoconstriction [34].

In the case of bronchiolar wall thickening, edema and predominant intraluminal filling by inflammatory exudate or mucus, the abnormal bronchioles become visible on HRCT. Intraluminal filling gives rise to branching opacities that end distally to clusters of well-defined nodules (tree-in-bud configuration) [31,35,36]. Depending on the plane, with respect to the long axis of these structures, the opacities may take V or Y shapes (Figure 5A & B) [37]. Individual nodules seen in these cases are clearly centrilobular [38]. More central bronchial wall thickening and bronchiectasis with various degrees of luminal plugging may also be seen [39]. This combination of findings takes a diffuse form in infectious bronchiolitis [35], in the context of any etiology of diffuse bronchiolectasis/bronchiectasis, and in diffuse aspiration bronchiolitis (Figure 5A–F) [3,37,40]. In nondiffuse infectious bronchiectasis and in patchy infectious bronchiolitis, the pattern may be more localized [41–43]. Diffuse tree-in-bud associated with central bronchiectasis is suggestive of ABPA, while a uniform diffuse pattern in the proper clinical and epidemiological setting suggests diffuse panbronchiolitis. Unusual causes of tree-in-bud have been reported in several conditions such as cellulose embolization, neoplastic emboli and psyllium inhalation [44].

Inflammatory processes of the bronchiolar walls and adjacent alveoli may result in centrilobular and perivascular distribution of ill-defined nodules without branching opacities or tree-in-bud configurations [45]. Although it is not unique to the following disorders, this pattern suggests hypersensitivity pneumonia, RB, RB-ILD and inhalational bronchiolitis. Due to their centrilobular location, these nodules do not abut the visceral pleura but are at a distance of 5–10 mm from it. In nonsmokers, this pattern suggests a subacute form of hypersensitivity pneumonia while in smokers, it may indicate RB or RB-ILD (Figure 5E) [37]. These conditions are usually associated with ground-glass opacities, especially in RB-ILD, with a predilection for the upper lobes where ground-glass opacities may coexist with emphysema. The differential diagnosis should include PLCH, in which centrilobular nodules are more prominent and well defined with irregular borders. Cavitations in some of the nodules further suggest PLCH before taking the typical form of irregular shaped cysts and nodules.

Bronchiolar narrowing due to proliferation of granulation tissue or fibrosis causes air trapping and hyperlucent lungs with or without mosaic attenuation (Figure 5F). Mosaic attenuation describes the coexistence of relatively decreased attenuation areas with areas of apparently 'increased' lung density, that do not obliterate the underlying structures, whose borders are well defined, frequently resulting in a geographic pattern that suggests constrictive-obliterans bronchiolitis. These are low-density areas that are abnormal mainly due to hypoxic vasoconstriction, and in well-established disease due to oligemia, and expiratory slices reveal regional air trapping. Expiratory images assist in the differential diagnosis from diffuse parenchymal disease causing mosaic attenuation. The combination of lobular areas of ground-glass opacities, normal lung opacity and lobular areas of reduced attenuation (mosaic perfusion), the so-called 'headcheese sign' [28], more or less associated with ill-defined centrilobular nodules, could be seen in hypersensitivity pneumonia, RB-ILD associated with desquamative interstitial pneumonia (DIP), sarcoidosis and 'atypical' pneumonia [46]. Low-attenuation lobular areas without additional features in HRCT suggest constrictive-obliterans pattern bronchiolitis as observed in toxic fumes and gases bronchiolitis, drug toxicity, BOS, cryptogenic constrictive bronchiolitis and occasionally in DIPNECH.

## PFTs in bronchiolitis

Independent of the exact cause of bronchiolitis, the smaller bronchi and bronchioles are the main site of airway obstruction, leading to airflow limitation due to wall thickening and lumen obliteration by inflammatory and fibrosing tissue [47]. Owing to the large number of small airways and bronchioles, a great percentage among them could be narrowed or totally obstructed without a significant loss of lung function and therefore normal PFTs may
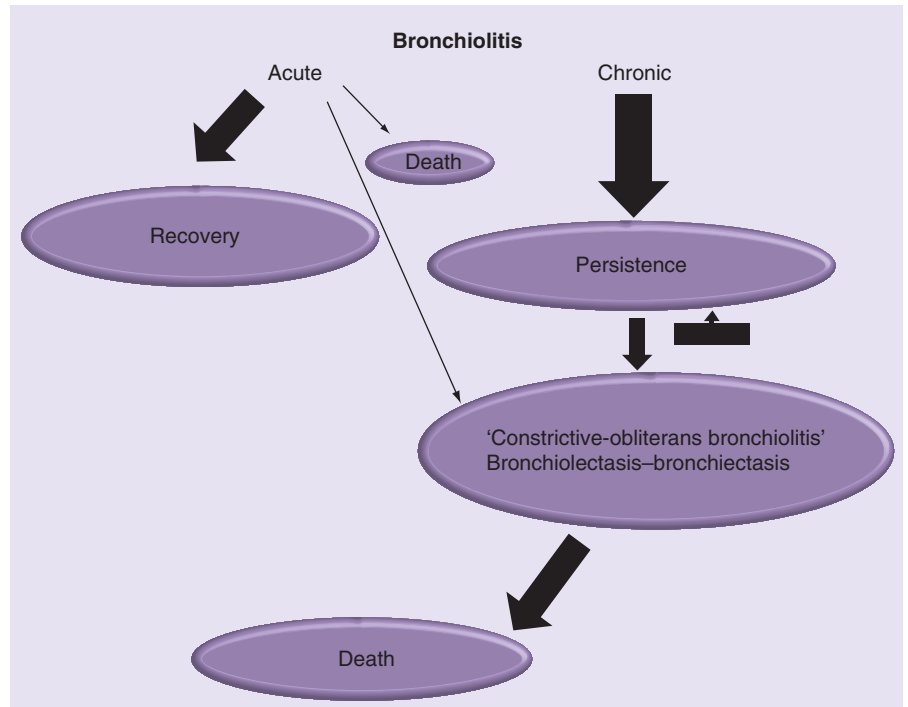
persist despite already established small airways disease [48]. On the other hand, if any-cause acute or chronic bronchiolitis progresses to severe diffuse airway narrowing and/or distortion may result in severely impaired PFTs more or less rapidly. The exact pattern of impairment (obstructive, restrictive or mixed) relates to several factors and among them, the primary cause of bronchiolitis and whether it occurs as an idiopathic or secondary form of disease and its prominence or coexistence with changes in the rest of the alveolar structures of the secondary lobule. Indeed, a mixed obstructive and restrictive pattern is not uncommon if the bronchiolar component coexists with changes in the peribronchiolar alveolar structures [1]. Air trapping commonly occurs in diffuse bronchiolitis as well as a reduced diffusing capacity [3]. With the exception of bronchial asthma, bronchodilators have no significant effect on PFTs [49]. Forced expiratory flow at 25–75% ($FEF_{25-75\%}$) of forced vital capacity is not considered more reliable than forced expiratory volume at 1 s ($FEV_1$) for the early detection of small airways obstruction [50]. The change of slope in phase III of the single-breath nitrogen washout test could be used as an early marker of bronchiolar obstruction [50].



**Figure 2. Bronchiolitis may present clinically as acute or chronic.** Most of the acute bronchiolitis cases, as shown on the left, recover spontaneously or after treatment. Very few may be severe enough to lead to death. Occasionally, acute bronchiolitis may evolve to diffuse bronchiolar cicatrization (scarring) and its consequences (constrictive-obliterans bronchiolitis, bronchiolectasis–bronchiectasis, McLeod syndrome). Chronic bronchiolitis may persist indefinitely (reverse arrow) or even evolve to constrictive-obliterans bronchiolitis with/or without bronchiolectasis–bronchiectasis. Any-cause diffuse bronchiolar scarring may lead to progressive and irreversible small airways obstruction, respiratory failure and death.

## Secondary bronchiolitis
### Pulmonary infections

Infections are the most common clinical conditions leading to bronchiolitis, and can be isolated, prominent or coexistent with microbial inflammation of the rest of lobular alveolar structures. In the latter case, abnormalities involve individual lobules or groups of lobules in their entirety, while adjacent lobules appear normal. Lobular consolidation or ground-glass opacities, often confluent, are the main imaging findings and direct or indirect findings of small airways involvement are overshadowed by the above mentioned panlobular abnormalities. Bronchopneumonia better defines the above description and begins as an infectious inflammation of the bronchioles rapidly extending into the surrounding alveolar spaces. Virtually all bacteria and fungi, as well as many viruses, may cause bronchopneumonia [5,51].

Bronchiolitis is the most common form of isolated acute viral small airways infection affecting infants and young children [52]. The disease presents as acute respiratory illness with coryza, cough and low-grade fever progressing to tachypnea, chest hyperinflation and retractions and widespread crackles or wheezes. Respiratory syncytial virus is the main cause. Parainfluenza viruses type 1, 2 and 3, adenoviruses, several other viruses and *Mycoplasma pneumonia* may also be involved.

In the most severe cases, the disease is characterized histologically by extensive bronchiolar respiratory epithelium necrosis and small airways obstruction from various cellular debris and fibrin. Lymphoid follicles and lymphocytic bronchiolar infiltrates are commonly observed. If severe, the disease may lead to respiratory insufficiency and death [53], but the majority of cases recover without sequelae. In some children, recurrent wheezing or even bronchiolitis obliterans may ensue. Treatment options include inhaled epinephrine, oxygen therapy and fluid replacement [54]. Palivizumab, the first humanized murine monoclonal anti-F glycoprotein immunoglobulin with neutralizing and fusion inhibitory activity against respiratory syncytial virus, reduces hospitalizations in infants with a history of prematurity or cardiopulmonary disease [55].

Adenoviral bronchiolitis in infancy may lead to severe bronchiolitis obliterans which, in case of involvement of one lung, is manifesting in adulthood with unilateral hyperlucent lung – Swyer–James (MacLeod) syndrome [56]. The disease may also present with localized, unilobar or bilateral hyperlucency. Lobular hypoplasia and panlobular emphysema related to early infancy occurrence of bronchiolitis obliterans constitute the underlying lesion. Bronchiolectasis–bronchiectasis commonly coexists.

Probably the most paradigmatic form of bacterial bronchopneumonia is that of *Staphylococcus aureus*. Infection begins at

**Figure 3. Secondary pulmonary lobule, as shown by Miller** [27]. The diagram shows secondary pulmonary lobule from the lung periphery surrounded by connective tissue septa and pulmonary vein branches. The airway anatomy from the level of the lobular bronchiole to lung periphery is shown. The large circle shows the approximate size of an acinus. The smaller circle shows the approximate size of a primary pulmonary lobule as defined by Miller. The pulmonary artery branches are shown as thick black structures. Reproduced with permission from [28].

the level of the small bronchioles and the peribronchiolar alveolar structures, rapidly involving the adjacent lobular structures in a confluent manner. Small peribronchiolar abscesses may form and may increase in size. Small airways obstruction may lead to pneumatocele formation most commonly in children. Pneumatoceles are thin-walled cavities, while abscesses are thick-walled cavities with irregular inner surface secondary to parenchymal necrosis. Small airways involvement is easier to appreciate on HRCT scan of the chest and manifests as centrilobular nodules or a 'tree-in-bud' pattern coexisting with lobular airspace shadows more or less confluent and/or one or multiple abscesses. Pneumatocele formation is also observed in the upper lobes of patients with AIDS and *Pneumocystis jiroveci* pneumonia [57–59]. Pneumatocele formation relates to several mechanisms such as bronchiolar obstruction and check-valve mechanism leading to localized emphysema, cavitation due to necrosis and parenchymal necrosis due to bronchiolar obstruction and check-valve mechanism. In case of communication of the bronchiolar lumen with the interstitium, subpleural blebs may form that present a high risk of pneumothorax formation [59].

One other form of bronchiolar infective involvement commonly occurs in reactivation tuberculosis [60–62]. Reactivation tuberculosis involves any lung segment and predominates in the apical and posterior segments of the upper lobes or the superior segments of the lower lobes. The typical parenchymal pattern is that of an airspace consolidation more or less confluent. Cavitation occurs

in approximately 40% of cases. Cavities are commonly associated with bronchogenic spread of the disease. In this case, endobronchial disease of the distal draining bronchi-bronchioles occurs frequently and is commonly observed in resected lung specimens. Bronchiolectasis–bronchiectasis may ensue. On HRCT scans of the lungs centrilobular nodules and/or 'tree-in-bud' are commonly observed and accompany cavitations and bronchiectasis [36]. Upper lobe bronchiectasis in tuberculosis are commonly 'dry' bronchiectasis and may manifest with hemoptysis.

Finally, bronchiolectasis filled with purulent secretions and transmural inflammatory infiltrate, mucosal edema, ulceration and neovascularization is common in almost any-cause bronchiectasis. Indeed, dilated bronchi and bronchioles are visible all the way to the pleural surface on surgical resected or autopsied lungs. Furthermore, in most cases, bronchiectasis, bronchiolitis–bronchiolectasis may be the earlier phase of airway wall damage, whereas secretions stasis as well as recurrent infections, the so-called 'vicious cycle' of Cole and coworkers [63], secondarily involve and damage the larger airways [64]. Among all-causes bronchiectasis, cystic fibrosis, an autosomal recessive disorder caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator protein, is the most paradigmatic [65]. Cystic fibrosis has a variable clinical picture and the most important manifestations are gastrointestinal and respiratory, the latter responsible for more than 80% of deaths. In the lungs, there is thick and tenacious mucus that obstructs the airways and predisposes to colonization and infection from pathogens such as *S. aureus* and *Pseudomonas aeruginosa* that perpetuate the vicious cycle of inflammation and infection, resulting in severe bronchiectasis and eventually in respiratory failure. Cystic fibrosis is an airway disease with no alveolar or parenchymal involvement. The disease starts in the small airways as presented in autopsy studies of infants and young children with cystic fibrosis that revealed increased diameter of the respiratory bronchioles and extensive bronchiolitis obliterans [66]. Neutrophilic inflammation in the bronchiolar wall and lumen is present even in the absence of infection during the first months of life. Thickening of the bronchioles with deposition of fibrous tissue and airway smooth muscle hypertrophy are well described in the natural history of the disease and relate to the severity of the airway inflammation [66].

### *Hypersensitivity disorders*
#### Bronchial asthma
Evidence of small airways inflammation (bronchiolitis) in asthma was established after the description of the pathology of asthma
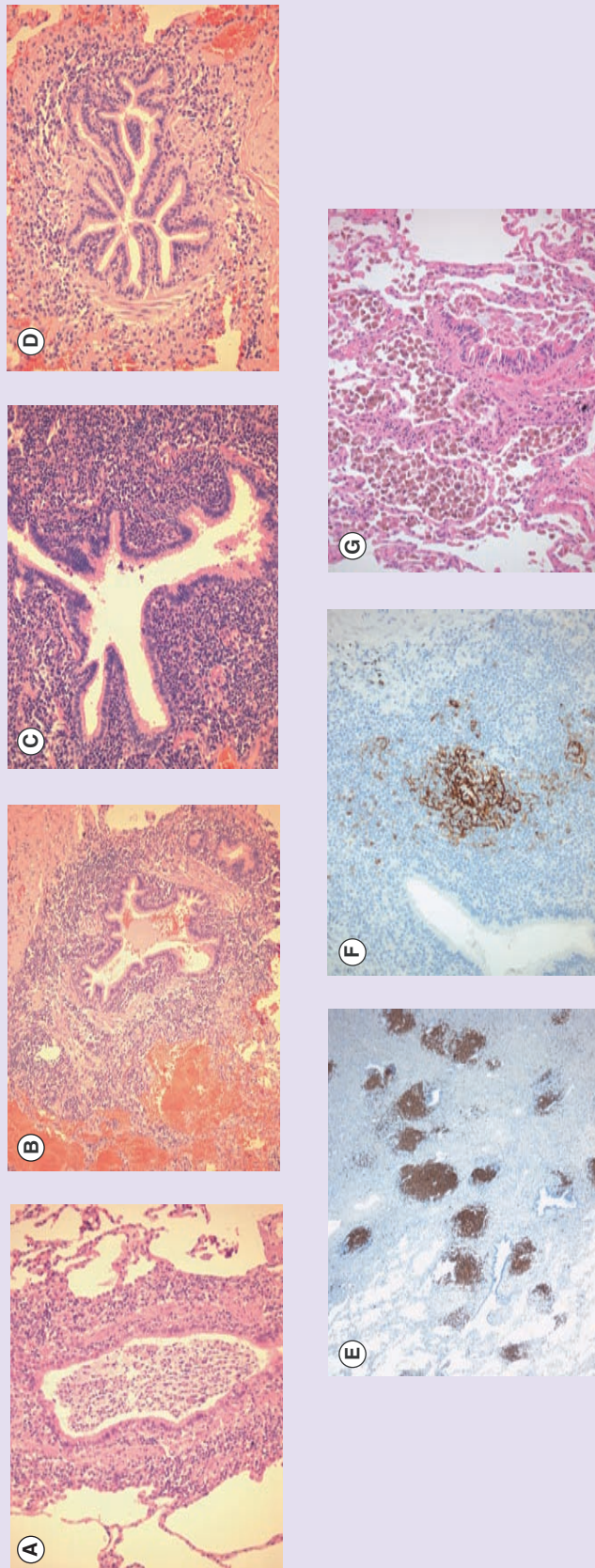
**Figure 4. Histopathological pictures of various forms of bronchiolitis. (A)** Acute infectious bronchiolitis (hematoxylin and eosin ×200). Chronic mononuclear cell infiltrate (lymphocytic bronchiolitis) around the small bronchiole in primary Sjögren's syndrome (hematoxylin and eosin ×100 **[B]** and ×200 **[C]**). **(D)** Bronchiolitis – constrictive pattern with peribronchiolar inflammation (hematoxylin and eosin ×200). **(E)** Follicular bronchiolitis. The lymphocytes show immunoreactivity for CD20 antigen (immunostaining ×40). **(F)** Follicular bronchiolitis. Expression of CD23 antigen by follicular dendritic cells (immunostaining ×200). **(G)** Respiratory bronchiolitis in a smoker and alveolar space occupied by desquamated type 2 alveolar pneumocytes (hematoxylin and eosin ×200).

death. At postmortem examination, bronchiolar walls appeared entirely involved by an inflammatory process characterized by goblet cell hyperplasia, epithelial necrosis and sloughing into the bronchiolar lumen in association with intraluminal mucus and several types of cellular debris, apparent thickening of the subepithelial basement membrane due to increased deposition of collagen fibrils and extracellular matrix beneath, increased smooth muscle and inflammatory eosinophilic and lymphocytic infiltrates throughout the entire thickness of the bronchiolar wall [6]. Similar pathological changes also occur in the large airways but the major site of airways obstruction lies in the peripheral airways in any asthma attack. Asthma deaths affect all age groups, occur mainly outside the hospital and may present in one of two ways: slow onset, late arrival events, the majority (80%) [67], and sudden onset fatal asthma [68,69]. The above described histopathological description refers to the postmortem examination in slow onset, late arrival asthma death. In the minority (20%) of sudden onset fatal asthma, pathological examination shows 'empty' airways (no mucoid impaction) and prevalence of neutrophils in the bronchiolar inflammatory infiltrate instead of eosinophils. A state of the art management practice is of paramount importance for patients with acute severe asthma [70]. *In vivo* studies in asthmatic patients have also shown that an inflammatory process characterized by infiltrating T lymphocytes and eosinophils is commonly observed also in mild asthmatics at the level of the bronchioles, suggesting that small airways inflammation is a key feature of the pathophysiology of asthma [71]. Finally, eosinophilic inflammation of the surrounding alveolar tissue has also been documented through transbronchial biopsies performed at 4:00 AM in nocturnal asthmatics [72]. In bronchial asthma bronchiolitis predominates, but also participates in the disease process of the entire bronchial tree and in specific clinical settings such as nocturnal asthma accompanies inflammation of the surrounding lobular alveolar structures [73].

Allergic bronchopulmonary aspergillosis
ABPA is a hypersensitivity reaction mainly to *Aspergillus fumigatus* antigens, clinically expressed as wheezing, fleeting pulmonary infiltrates with eosinophilia and bronchiectasis in either asthmatic or cystic fibrosis patients [7,74,75]. The same hypersensitivity reaction can
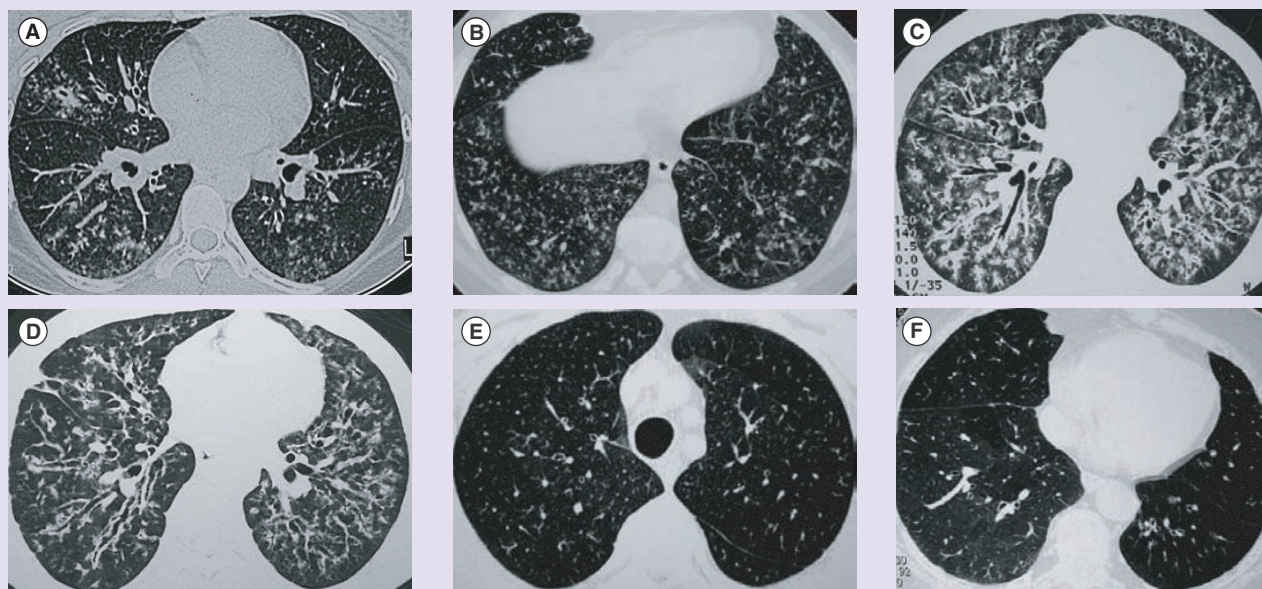
**Figure 5. High-resolution computed tomography pictures of various forms of bronchiolitis. (A)** Infectious bronchiolitis by respiratory syncytial virus. There is thickening of the walls of the subsegmental bronchi with ground-glass opacities and peribronchiolar small nodules. **(B)** Infectious bronchiolitis in a patient with severe asthma. The walls of the subsegmental bronchi are thickened, and in the periphery branching structures forming Y and V configurations with nodular opacities distally are clearly seen (tree-in-bud configuration). **(C)** Adenoviral bronchiolitis progressing to severe bronchiectasis and **(D)** bronchiolitis obliterans leading to death can be seen. In this case, peribronchial infiltrations predominate. After the acute phase, there are extensive bronchiectasis and in the periphery bronchial thickening and peribronchiolar nodular opacities are seen, representing bronchioles full of secretions. **(E)** Respiratory bronchiolitis-associated interstitial lung disease in a 37-year-old heavy smoker. There is mild bronchiolar wall thickening and minimal centrilobular nodules associated with subtle ground-glass opacities. The findings are more prominent in the apices and may coexist with signs of emphysema. **(F)** Obliterative bronchiolitis is prominent in the left lower lobe. There is prominent oligemia (diameter of vessels smaller compared with the right side). The volume of the left lower lobe is decreased. In this patient, obliterative bronchiolitis was the end result of childhood viral bronchiolitis.

be caused by other fungal antigens (ABP-mycosis). In ABPA type I (IgE mediated), type III (immune complex mediated) and type IVb (T lymphocyte mediated) immune responses coexist [76]. ABPA is characterized pathologically by mucoid impaction that distends the bronchi and bronchioles causing ulceration and thinning of their wall leading to bronchiolectasis–bronchiectasis [74,75]. The above mentioned immunological processes that damage and induce remodeling of both the large (central bronchiectasis) and small airways result in end stage bronchiectasis and fibrobullous disease of the lungs. Other characteristic pathologic features of ABPA, except those of bronchial asthma, are eosinophilic pneumonia and bronchocentric granulomatosis.

Bronchocentric granulomatosis
Bronchocentric granulomatosis is an unusual pathologic entity characterized by replacement of bronchioles by necrotizing granulomatous inflammation, related in 50% of cases to hypersensitivity to several fungi and especially *A. fumigatus* [8]. Most patients also fulfill criteria of ABPA. The identification of fungal hyphae in the granulomatous inflammation confirms the diagnosis [8]. Bronchocentric granulomatosis has also been reported to occur in association with other infections, autoimmune conditions or

remains of unknown etiology [77]. The pathogenesis of the disease is poorly understood. Some authors advocate that bronchocentric granulomatosis should not be considered a distinct clinical entity, but rather an immunopathologic complication that may accompany several clinical conditions. This fact and the variety of etiologies are of paramount importance regarding therapeutic decisions [77]. Finally, bronchiolitis in bronchocentric granulomatosis is commonly patchy and localized and bronchioles involvement in chest imaging examination is usually overshadowed by the accompanying inflammatory changes that occupy the rest of the lobular structures.

Hypersensitivity pneumonia
Hypersensitivity pneumonia is a complex immunologically mediated lung disease related to the inhalation at home or in the working environment of a multitude of antigens such as those derived from thermophilic bacteria, fungi, other bacteria or bacterial products, animal proteins, amoebae, insect products and less commonly chemicals [9]. The clinical presentation of the disease may be acute, subacute or chronic, although overlapping presentations may occur [78]. Histologically, hypersensitivity pneumonia early on presents as a peribronchiolar inflammation rich of germinal lymphoid follicles, along with chronic interstitial pneumonia that

involves the peribronchiolar alveolar structures. Lymphocytes are the majority of infiltrating cells. Small, non-necrotizing granulomas are commonly observed and tend to be loosely formed and poorly circumscribed. Foci of bronchiolitis obliterans and areas of BOOP-like reaction coexist. Foamy macrophages related to bronchiolar obstruction are present. Interstitial fibrosis maintaining the peribronchiolar accentuation becomes prominent in advanced disease [79]. In this stage, differentiation from usual interstitial pneumonia can be difficult. In hypersensitivity pneumonia, bronchiolitis almost always exists in both acute and chronic forms (bronchiolitis obliterans pattern) and accompanies early and advanced (honeycomb pattern) stage of interstitial involvement. Avoidance of exposure and corticosteroids constitute the main therapeutic strategy.

### Chronic eosinophilic pneumonia

CEP is a rare disorder of unknown cause, characterized by the progressive onset of respiratory symptoms, bilateral pulmonary infiltrates with peripheral and upper lobe predominance and alveolar and/or blood eosinophilia. The major histopathologic feature of CEP is the infiltration of the lung parenchyma by eosinophils and macrophages preserving the lung architecture [10]. Bronchiolar involvement in CEP may present as proliferative bronchiolitis characterized by buds of loose organizing connective tissue within air spaces overfilling bronchioles (BOOP-like reaction) [10] or in a similar manner as in asthma since bronchial asthma coexists in the majority of patients with CEP.

### Eosinophilic granulomatosis & polyangiitis (Churg–Strauss syndrome)

Eosinophilic granulomatosis and polyangiitis (Churg–Strauss syndrome) is an uncommon systemic vasculitis characterized by the combination of bronchial asthma, peripheral blood eosinophilia (>1500/μl) and evidence of vasculitis involving two or more extrapulmonary sites (mainly skin lesions, peripheral neuropathy, serositis and heart failure). Glomerulonephritis is uncommon and usually mild. Antineutrophil cytoplasmic antibodies are detected in up to 70% of patients. Histologic changes in the lung include the combination of eosinophilic pneumonia, granulomatous inflammation and necrotizing vasculitis [11]. The disease is thought to progress in three phases: asthma, eosinophilic pneumonia and vasculitis, although this is not always the case [80]. In the asthma phase, bronchiolitis is the one formerly described in the asthma section. In the eosinophilic pneumonia phase, eosinophils infiltrate alveolar spaces. In the vasculitis phase, granulomatous vascular necrosis or only eosinophilic vasculitis may present [80]. Extravascular granulomas occasionally involving the bronchiolar wall, fibrinoid necrosis and vascular thrombotic lesions are commonly observed [81]. Treatment consists of glucocorticosteroids with or without immunosuppressants.

### *The spectrum of smoking-related disorders*

#### Bronchiolitis in COPD

Although COPD encompasses several clinical expressions and/or histopathological lesions, RB is almost always present, and may become progressive and severe enough to determine dismal prognosis. This is in relation to the fact that damaged bronchioles become the major site of airways obstruction in COPD [12]. Tobacco smoking, the major risk factor for COPD, induces RB, an inflammatory immune reaction in the lower airways of every smoker even in those not fulfilling criteria for COPD. In COPD, this inflammatory immune response is amplified. Tobacco smoke inhalation induces epithelial disruption, leading to reduced clearance of secretions and inflammatory mucous stasis in the small airway lumen. Furthermore, inflammatory cells infiltrate the airway wall, where both innate and adaptive inflammatory immune responses participate, forming lymphoid follicles (bronchus-associated lymphoid tissue [BALT] hyperplasia). Adaptive immune response is also driven by microbial colonization and infection. These lesions couple with a repair or remodeling process where connective tissue is laid down in the adventitia of the small airways wall (peribronchiolar fibrosis). The above lesions thicken the airway, reduce lumen caliber and restrict their opening upon inspiration [82]. This remodeling process not only narrows small airways but also removes a large number of bronchioles even before the emphysema appearance [83]. Emphysema is also associated with a similar inflammatory infiltrate found in the airways and further adds to the small airways obstruction by reducing elastic recoil forces necessary to drive air out of the lungs [84]. However, in both centrilobular and panlobular emphysema, bronchiolitis pre-exists and leads to widespread narrowing and loss of small airways before their onset [83]. Finally, the histologic features associated with tobacco smoking-related bronchiolitis are nonspecific and overlap with other types of bronchiolitis [85].

### Respiratory bronchiolitis interstitial lung disease

Tobacco smoking-related RB exists in every smoker even in the absence of any clinical manifestation [13]. In such cases, RB is characterized by the accumulation of golden-brown pigment-laden macrophages within and/or around respiratory bronchioles. Sparing of the peribronchiolar lobular alveolar structures is present [86]. Occasionally, RB may become more extensive and prominent, and produces symptoms, physiologic abnormalities and imaging features suggestive of bronchiolar involvement, defining a clinical entity named, probably inappropriately, RB-ILD and included among the ILDs [87], although a smoking-related RB. Although some controversy still exists about their relationship as a spectrum of diseases relating to tobacco smoking, in some patients, the above described macrophages increase in numbers and extensively occupy the lobular alveolar spaces, defining a clinical entity named desquamative interstitial pneumonia (DIP). The term is a misnomer because macrophages originally were considered desquamated type 2 alveolar pneumocytes. Also, DIP is included among ILDs although it is not a fibrogenic ILD but a smoking-related alveolar space occupying macrophage-related inflammatory lesion. Occasionally, mild interstitial fibrosis may be observed but should probably not be considered as the fibrogenic evolution of the above but as the coexistence of the recently described smoking-related interstitial fibrosis [88,89]. Regarding management

strategies, smoking cessation is imperative to arrest progression. Corticosteroid therapy offers modest clinical benefit [90]. Occasionally in patients with rapidly progressive or fulminant DIP, corticosteroids plus immunosuppressants proved decisive to obtain remission [91].

Pulmonary Langerhans cells histiocytosis

PLCH is a tobacco smoking-related bronchiolocentric disease, equally affecting young men and women in their third and fourth decades [14,92]. Histologically, it is characterized by peribronchiolar accumulation of CD1a+ Langerhans cells, eosinophils, macrophages and lymphocytes forming nodules at the level of the bronchioles. The above lesions progress from cellular nodules to cellular and fibrotic nodules to entirely fibrotic scars with stellate shape appearance totally obliterating the bronchiolar lumen and leading to fibrocystic deformation of the supplying parenchyma. Cavitation of cellular nodules may be seen and may relate to both an airway remnant or *de novo* cavitation of enlarged nodules. The HRCT reveals centrilobular nodules with or without cavitation and cysts (irregular emphysema) in various combinations. Lung bases are relatively spared. Smoking cessation is imperative. Cladribine has been used as salvage therapy with dubious results. RB, RB-ILD, DIP and PLCH may coexist in some patients in relation to their common tobacco-smoking etiology [93].

### Bronchiolitis related to toxic fumes & gases inhalation

A number of irritant gases and fumes have been associated with lung injury. The type and severity of this injury and the clinical presentation are determined by the solubility and concentration of the gas, and the duration of exposure. Low levels of highly soluble gases, such as sulfur dioxide, chlorine gas, ammonia or less soluble gases, such as nitrogen dioxide, phosgene, photochemical air pollutants and ozone, could pass into peripheral airways and reach the bronchioles. After exposure, three clinical phases may develop. In the first, acute phase, during milder exposures, patients may be asymptomatic or develop upper respiratory symptoms persisting for hours, days or weeks. At high concentrations of exposure, some patients develop pulmonary edema and acute respiratory distress syndrome (ARDS), and death may occur [15]. Recovery without long-term sequelae is usual in this phase in the absence of ARDS. Patients who progress to the second phase may experience a mixed type of damage relating to both the sequelae of fibroproliferative phase of ARDS and/or the developing constrictive bronchiolitis relating to the specific irritant. Patients who recover from earlier phases may enter a third chronic phase characterized by the development of severe and irreversible constrictive bronchiolitis [94]. Glucocorticosteroid administration may prove useful in any phase although their efficacy diminishes from the early to the late phases of damage [95]. In nitrate exposure, the presence of methemoglobinemia must be considered and methylene blue should be administered. Other substances causing bronchiolitis obliterans when inhaled are well described in the case of 'popcorn lung' where the damage is caused by the food additive diacetyl [96]. In toxic fumes and gases, inhalation bronchiolitis becomes prominent and defines a clinical entity of known etiology as bronchopulmonary lung damage evolves to chronicity and is focused on bronchioles.

### Diffuse aspiration bronchiolitis

Chronic oropharyngeal and/or gastric aspiration may lead to several lung reactions such as aspiration pneumonia, aspiration pneumonitis (Mendelson's syndrome), lipoid pneumonia, lung abscess eventually associated with empyema, *Mycobacterium fortuitum* pneumonia, diffuse aspiration bronchiolitis and less probably idiopathic pulmonary fibrosis [16,97–100]. Aging, neurological disorders, laryngectomy, obesity and esophageal disorders associated or not with clinically evident gastroesophageal reflux are risk factors. Diffuse aspiration bronchiolitis is an unrecognized clinical entity related to chronic occult aspiration characterized by persistent cough, dyspnea and recurrent pneumonias. On chest radiographs, an interstitial pattern is evident, shown to be centrilobular nodules with associated 'tree-in-bud' appearance on HRCT. Histopathologically, a bronchiolocentric organizing pneumonia process is apparent with giant cells granulomas containing material compatible with food, commonly associated with areas of acute bronchopneumonia. Surgical lung biopsy is necessary to obtain enough tissue for diagnosis. The granulomatous inflammation related to foreign material suggests that the bronchiolitis is related to the foreign body reaction and not to the acid aspirated injury. Treatment relates to measures necessary to reduce aspiration. In diffuse aspiration bronchiolitis, bronchiolar involvement predominates and defines a clinical entity of known etiology but also participates in disease process of surrounding peribronchiolar alveolar structures (acute bronchopneumonia or other aspiration disorder).

### Inhaled particle-induced small airways disease

Inhaled particle-induced small airways disease is seen in both workers with high-level occupational exposure to particles such as asbestos, coal, sheet silicates, aluminum oxide, iron oxide and silica, as well as in persons with environmental exposure to high levels of ambient particulate air pollutants [17]. The aforementioned particles preferentially deposit at the level of the membranous and respiratory bronchioles [101], inducing a fibrotic thickening and distortion of their walls as well as smooth muscle hyperplasia [102]. The airway lumen becomes distorted and often narrowed. Pigment deposition is almost always present. The development of centrilobular emphysema further contributes to airflow obstruction. In particle-induced small airways disease, bronchiolitis is prominent and defines a clinical entity of known etiology and may coexist with lesions of the peribronchiolar structures of the secondary pulmonary lobule (emphysema and/or fibrosis).

### Drug-induced bronchiolar toxicities

Several drugs have been reported to induce lung toxicity in the form of bronchiolitis (Table 1). Two different patterns of bronchiolar damage are encountered: BOOP–COP, the most common, and bronchiolitis obliterans. Some drugs have been reported to be responsible for both patterns of bronchiolar damage in different case reports. A BOOP–COP pattern of damage has been reported

to be related to antimicrobials such as minocycline, nitrofurantoin, cephalosporin, amphotericin B, daptomycin and abacavir; anticancer agents such as busulfan, methotrexate, bleomycin, doxorubicin, cytosine-arabinoside, cytarabine ocfosfate, chlorambucil, rituximab and oxaliplatin; cardiovascular agents such as amiodarone [103] and acebutolol; anti-inflammatory agents such as mesalamine, bucillamine and infliximab; immunosuppressive agents such as azathioprine, 6-mercaptopurine, tacrolimus, sirolimus and everolimus; anticonvulsants such as carbamazepine and phenyntoin and various others such as IFN-α, -β and -γ, hexamethonium, L-tryptophan, sulindac, ticlopidine, fluvastatin, venlafaxine, risedronate, free-base cocaine use and heroin [201]. A bronchiolitis obliterans pattern has been reported to be related to tiopronin, lomustine (CCNU) and self administration of the traditional medicine product *Sauropus androgynus* [201]. Both patterns of damage reported in different cases are related to sulfasalazine, penicillamine, busulfan and aurothiopropanosulfonate (gold) [201]. BOOP–COP

### Table 1. Drugs causing bronchiolitis.

| BOOP–COP | Bronchiolitis obliterans | BOOP–COP or bronchiolitis obliterans |
|---|---|---|
| Antimicrobials (minocycline, nitrofurantoin, cephalosporin, amphotericin B, daptomycin, abacavir) | Tiopronin | Sulfasalazine |
| | Lomustine | Penicillamine |
| Anticancer agents (busulfan, methotrexate, bleomycin, doxorubicin, cytosine arabinoside, cytarabine ocfosfate, chlorambucil, rituximab, oxaliplatin) | *Sauropus androgynus* | Busulfan |
| | | Aurothiopropanosulfonate (gold) |
| Cardiovascular agents (amiodarone, acebutolol) | | |
| Anti-inflammatory agents (mesalamine, bucillamine, infliximab) | | |
| Immunosuppressive agents (azathioprine, 6-mercaptopurine, tacrolimus, sirolimus, everolimus) | | |
| Anticonvulsants (carbamazepine, phenyntoin) | | |
| Various others (IFN-α, -β and -γ, hexamethonium, L-tryptophan, free-base cocaine use, sulindac, ticlopidine, heroin, fluvastatin, venlafaxine, risedronate) | | |

BOOP: Bronchiolitis obliterans organizing pneumonia; COP: Cryptogenic organizing pneumonia.

damage may be reversible with drug withdrawal, although in some patients glucocorticosteroids administration may be necessary. Bronchiolitis obliterans damage is much more severe, does not respond to any treatment and leads to irreversible severe airways obstruction and death.

### Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown etiology, most commonly affecting the lungs, the chest nodes, the skin and the eyes [18,104]. In the lungs, granulomas can be located anywhere in the interstitial parenchyma including the vascular wall, the pleura, and mainly along lymphatic pathways, in the perilobular area as well as in centrilobular peribronchiolar sites. Indeed, in HRCT of the chest, thickened bronchovascular bundles constitute the most common finding. In patients with sarcoidosis, bronchiolitis recovers spontaneously in most cases, as is usual for sarcoidosis in general, or may respond to corticosteroid treatment. However, it may also evolve towards fibrosis and bronchiolar lumen obliteration responsible for bullous and bronchiectasis formation that characterize most of the stage IV fibrobullous sarcoidosis. Although sarcoidosis is an unknown etiology disease, it constitutes a clearly defined clinical entity, justifying the inclusion of its bronchiolar involvement among the secondary cause bronchiolitis.

### Neoplasms

Bronchioles may be involved in neoplasms both directly or as a paraneoplastic manifestation (**Box 3**). Lung cancer may develop both in the primary bronchus, small bronchioles and alveoli. Mostly, adenocarcinoma, large cell cancer, spindle cell typical carcinoids and atypical carcinoids are encountered in the peripheral part of the lung. Preneoplastic lesions such as squamous dysplasia and carcinoma *in situ* may be present into the bronchiolar epithelium. In the parenchyma, close to lung cancers, bronchioles may present filled with a mixture of macrophages and acute inflammatory cells. Pulmonary lymphangitic carcinomatosis is a metastatic lung disease characterized by the diffuse infiltration and obstruction of the pulmonary parenchymal lymphatic system both peribronchiolar as well as interlobular septal by tumor cells. The most common underlying primary tumors are breast, stomach and lung cancers [105].

Primary pulmonary lymphomas are rare extranodal forms of lymphoid neoplasia and arise from BALT [106]. Extranodal marginal zone B-cell lymphoma of BALT-type represents the most common primary pulmonary lymphoma, is classified as a distinct subgroup of non-Hodgkin's lymphomas and is associated with autoimmune disorders or other chronic inflammatory processes [107]. Lymphomatoid granulomatosis is a rare, angiocentric and angiodestructive, Epstein–Barr virus-driven, T-cell-rich B-cell lymphoproliferative disorder with clinical presentation varying from an indolent process to an aggressive B-cell lymphoma. Lungs are most commonly involved and bronchioles are ulcerated or obliterated by granulation tissue [108].

Malignant histiocytosis, a subset of histiocytic sarcoma, is a systemic disease characterized by infiltration with abnormal histiocytes and pursues a very aggressive course that may lead to death.

## Box 3. Bronchiolitis in neoplasms.

**Neoplasms**

- Pulmonary lymphangitic carcinomatosis (breast, stomach, lung cancers)
- Primary pulmonary lymphomas
- Extranodal marginal zone B-cell lymphoma
- Lymphomatoid granulomatosis
- Malignant histiocytosis

**Paraneoplastic syndromes**

- Paraneoplastic pemphigus

Pulmonary infiltration follows the normal lymphatic pathways of the lung, and in some cases, there is a marked predilection of the infiltrate to occlude small airways called 'malignant histiocytosis bronchiolitis' [109].

Paraneoplastic pemphigus is a rare autoimmune disease with poor prognosis, associated with underlying neoplasia (overt or occult) and characterized by painful erosive lesions and blisters involving the oral, nasal, upper gastrointestinal, respiratory, ocular and genital epithelium. Associated neoplasia (non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease, thymoma, retroperitoneal sarcoma, Waldenström macroglobulinemia) is a requisite finding of paraneoplastic pemphigus. In approximately 30% of patients, bronchiolitis obliterans ensues, leading to progressive respiratory failure. It has been suggested that IgG antibodies against the plakin group of proteins and CD8$^+$ T cells are responsible for the inflammatory response in the bronchioles [110].

## Idiopathic (primary) bronchiolitis
### Cryptogenic constrictive bronchiolitis

Cryptogenic constrictive bronchiolitis, also termed idiopathic bronchiolitis obliterans, is an extremely rare, purely bronchiolar disorder without accompanying lesions involving the peribronchiolar lobular structures [1]. It occurs most commonly in middle-aged nonsmoking women and presents with unproductive cough and progressive dyspnea on exertion [19]. The chest roentgenogram is normal or shows hyperinflation and the HRCT may confirm air trapping. Surgical lung biopsy is necessary to ensure diagnosis. Pathologically, it is characterized by patchy areas of peribronchiolar fibrosis resulting in extrinsic constriction of the airway lumen until complete obliteration [111]. Mucus stasis is commonly observed. Few cases have been reported. Glucocorticosteroids, bronchodilators and macrolides proved disappointing. Some patients progress to respiratory failure and death.

### Diffuse panbronchiolitis

Diffuse panbronchiolitis is a unique form of diffuse bronchiectasis-associated COPD of unknown etiology, quite exclusively occurring in Asians, primarily Japanese individuals [20,112]. 'Diffuse' refers to the bilateral distribution of the disease and 'pan' refers to the inflammatory involvement of all layers of the respiratory bronchiole [113]. The disease is also encountered in Taiwan, Korea, China, Malaysia, Thailand and Singapore. Rare cases

have also been reported in Caucasians, Hispanics and African–Americans [114–116]. Histologically, the disease is characterized by the triad of mixed inflammatory infiltrate affecting the respiratory bronchioles, follicular bronchiolitis (BALT hyperplasia) and accumulation of foamy macrophages in the interstitium and surrounding alveoli. Damage to the bronchiolar epithelium and wall promotes the development of bronchiolectasis leading to diffuse severe bronchiectasis colonized by *Haemophilus influenzae* and *P. aeruginosa*. The etiology is unknown but a genetic susceptibility unique to Asians and an environmental factor restricted in this geographic area should play a role (the disease is rare in Asians living abroad). Patients present with symptoms of both the upper and lower airways (sinusitis is almost always present) and progressive dyspnea on exertion as airway obstruction deteriorates. Most patients also present high titers of serum cold agglutinins. HRCT initially shows bilateral centrilobular nodules with or without air trapping beginning from the lower lung zones and extending to the entire lung, ending with diffuse bronchiectasis. The prognosis of diffuse panbronchiolitis dramatically changed with the long-term oral administration of macrolides acting mainly as immunomodulators, plus antibiotics in the case of infective exacerbations. Some patients, despite treatment, progress to respiratory failure and death.

### Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Neuroendocrine epithelial cells of the airways may occur either as solitary cells or small well-defined innervated clusters supported by Clara cells, called neuroepithelial bodies. In the human airways, neuroendocrine cells, though infrequent after birth, are more numerous in the small bronchi and proximal bronchioles. Neuroendocrine epithelial solitary cells and bodies contain electron-dense granules that are characterized by amine-handling capacities and are considered to be members of the amine precursor uptake and decarboxylation cells series or the paraneuron family [117]. Bombesin and gastrin-releasing peptide are detected in human pulmonary neuroendocrine cells and both have the same physiological effects, the reason for being collectively called 'bombesin-like peptides' [118]. Both peptides are growth factors for bronchial epithelial cells, pulmonary fibroblasts, smooth muscle and lung cancer cell lines and may lead to peribronchiolar fibrosis. Secondary pulmonary neuroendocrine cell hyperplasia is associated with living at high altitude, cigarette smoking and several chronic lung diseases such as pulmonary Langerhans cells granulomatosis, cystic fibrosis, infants with bronchopulmonary dysplasia, asthma, diffuse panbronchiolitis and COPD. The occurrence of diffuse hyperplasia of the pulmonary neuroendocrine cells in the absence of the above described conditions (idiopathic) defines a new clinical entity recently described, called DIPNECH [21]. Hyperplasia of neuroendocrine cells above the basement membrane may take the form of generalized proliferation of scattered neuroendocrine cells, small nodules or linear proliferation [119]. If hyperplastic neuroendocrine cells extend beyond the basement membrane, they are termed tumorlets and can be localized or diffuse. Nodules greater than 5 mm are classified as

carcinoid tumors. DIPNECH defines an idiopathic clinical entity because in some patients it leads to diffuse bronchiolitis obliterans as the prominent and/or isolated histopathologic feature, probably related to the growth effect of gastrin-related peptides on bronchiolar fibroblasts. The majority of patients presenting with DIPNECH are middle-aged nonsmoking women complaining of progressive exertional dyspnea and cough [120]. Physiological and imaging studies are compatible with small airways disease. To obtain diagnosis surgical lung biopsy is necessary. Some patients remain stable but others progress to severe respiratory failure and death. Associations with carcinoid tumors and clinical endocrinopathies have been reported with DIPNECH. A few tens of patients have so far been described and DIPNECH, although it is being recognized with increasing frequency, remains a rare and untreatable disease.

NEHI is an even more rare disorder recently described in infants with persisting tachypnea, hypoxemia and lung crackles, evaluated for ILDs [22]. Air trapping and ground-glass opacities are evident on HRCT. The disease is unresponsive to corticosteroids and bronchodilators. On surgical lung biopsy specimens, histochemical and immunohistochemical studies have shown an increased number of bronchiolar neuroendocrine cells. Patchy inflammation and fibrosis were observed only in a small proportion of the airways. Despite significant pulmonary morbidity, infants with NEHI gradually improve over time [121].

### Bronchiolitis obliterans syndrome

Post-lung transplantation BOS is characterized by the development of progressive small airways obstruction and is the leading cause of late mortality in these patients. BOS appears usually 1 year after transplantation, affects more than 50% of patients at 5 years and has a mortality greater than 50% [23]. The histologic picture of BOS is called bronchiolitis obliterans and is a form of chronic lung allograft dysfunction. Histologically, BOS in its early phase presents submucosal lymphocytic inflammation and disruption of the epithelium of bronchioles that is later accompanied by the ingrowth of fibromyxoid granulation tissue, which organizes in a cicatricial pattern, resulting in partial or complete obliteration [122,123]. In some instances, the only residual histologic evidence of BOS is a ring of circumferential elastin around an otherwise undetectable airway that is termed 'vanishing airways disease' [122]. BOS is a patchy process and transbronchial biopsy may fail to obtain diagnosis. The need for pathological diagnosis is obviated and is replaced by criteria based on the decline of post-transplantation $FEV_1$ and $FEF_{25-75}$, after excluding other causes of airway obstruction [122]. The pathogenetic mechanisms of bronchiolitis obliterans consist of alloimmune T-cell reactivity, antibody-mediated rejection (donor-specific HLA antibodies and non-HLA antibodies), autoimmunity to type V collagen and other self-antigens, and the activation of innate immunity in response to environmental and endogenous insults [23].

BOS can also complicate allogeneic hematopoietic cell transplantation in a small minority of cases (2–3%) and is a form of chronic graft-versus-host disease affecting the lung [124]. The histologic picture is the same as in bronchiolitis obliterans after lung transplantation. Augmentation or changing of immunosuppression, antimetabolites, calcineurin inhibitors, antilymphocyte and antithymocyte globulin, IL-2 receptor antagonists, methotrexate, cyclophosphamide, total lymphoid irradiation, extracorporeal photopheresis, alemtuzumab (humanized anti-CD52 antibody), azithromycin, infusion of donor bone marrow and finally retransplantation have been used for the treatment of BOS but unfortunately up to now, and despite some very encouraging data regarding azithromycin, none has proved totally effective in stopping or reversing the disease [125].

### Connective tissue disorders

Connective tissue disorders are unknown etiology systemic disorders affecting joints and muscles, as well as any other organ or tissue, and are associated with autoantibodies and/or autoreactive clones of T lymphocytes against 'self' molecules. Specific tissue damage relates to clinical expression. Lung involvement is common [24].

Primary Sjögren's syndrome is the one most commonly affecting the airways entirely [126–128]. Rhina sicca and xerostomia are related to mucous glands lymphocytic replacement both of nasal mucosa and major and minor salivary glands. Xerotrachea and xerobronchitis, as described by Henrik Sjögren are related to the same lymphocytic replacement of airways submucosal glands. Furthermore, large airways show an increased number of CD4+ T lymphocytes in the lamina propria [129]. The above lesions do not relate to PFTs abnormalities. Small airway obstruction is common and usually mild and relates to the presence of a chronic mononuclear cell infiltrate (lymphocytic bronchiolitis) around the small bronchioles often associated with BALT hyperplasia (follicular bronchiolitis). Severe airways obstruction related to chronic bronchiolitis is uncommon [130]. Follicular bronchiolitis is histopathologically characterized by aggregates of lymphoid tissue at the level of the small intralobular bronchioli often limiting their lumen. In such cases, through a 'check valve' mechanism, follicular bronchiolitis may lead to expiratory flow entrapment and bullae formation. Lymphocytic interstitial pneumonitis is histologically characterized by a diffuse alveolar infiltration of mature lymphocytes, mainly a population of polyclonal CD20 cells (B lymphocytes) in addition to other lymphoreticular elements such as plasma cells and other mononuclear elements including dendritic cells. Alveolar parenchymal lymphoid aggregates may be observed and commonly coexist with bronchiolar lymphoid follicles. Indeed, follicular bronchiolitis is considered by some as an early localized form of lymphoid hyperplasia. BALT is the hallmark of an adaptive immunity in course persisting to airborne antigenic stimulation and may lead to diverse grade of lymphoid hyperplasia, occasionally ending in lymphoid malignancy (marginal zone B-cell lymphoma of the lung or high-grade B-cell non-Hodgkin's lymphoma) [107] all arising in the bronchiolar wall. Rarely in primary Sjögren's syndrome does BOOP occur and occasionally bronchiolitis may coexist with interstitial disorders involving the entire lobular structure.

Rheumatoid arthritis is the connective tissue disorder most commonly associated with bronchiolectasis–bronchiectasis [131]. This respiratory complication presents several management problems in relation to the fact that these patients are colonized by microbes that, early during the disease course, become multiantibiotic drug resistant and drive patients to severe infective exacerbations. Certainly, immunosuppressive treatment with either classical drugs (e.g., methotrexate) or the new biological factors (e.g., anti-TNF antibody therapies) may increase the risk and the severity of serious infections [132]. Bronchiectasis adds a worse prognosis in rheumatoid arthritis; BOOP–COP pattern has also been described. This is the only manifestation of the airways that can be fully reversible by treatment. Pharmacologic management with azithromycin for several weeks may prove resolving. In nonresponding patients, glucocorticoids in medium doses (20 mg of prednisone) are usually effective. In case of BOOP–acute fibrinous organizing pneumonia, addition of mycophenolate mofetil may become necessary to obtain remission. Bronchiolitis obliterans is less common and the most severe of the airways manifestations in rheumatoid arthritis. Patients present progressive dyspnea on exertion and severe obstruction on PFTs, as well as hyperinflation without additional findings on chest roentgenograms. Bronchiolitis obliterans is an untreatable disease and leads to respiratory failure and death [133].

In systemic lupus erythematosus, bronchiolitis is rare and may present either as BOOP–COP or bronchiolitis obliterans. In systemic sclerosis, also, airways disease is extremely rare and very few cases of BOOP–COP are reported. In polymyositis–dermatomyositis, although rare, BOOP–COP is the most commonly observed pattern. In mixed connective tissue disease, which is the overlap of the above plus circulating autoantibodies to nuclear ribonucleoprotein antigen (anti-U1-Sn-RNP), although extremely rare, all of the above conditions may occur. In ankylosing spondylitis, apical fibrobullous disease is the main respiratory manifestation highly suggestive of small airways disease involvement but no studies exist to corroborate such an assumption. Follicular bronchiolitis has also been reported [134].

### Inflammatory bowel disease

In ulcerative colitis and Crohn's disease, respiratory manifestations are more frequent and heterogenous than generally appreciated [25,135]. Among them, airway abnormalities occur most commonly. The entire airway appears to be involved. Several forms of airways disorders have been described such as constrictive bronchiolitis, diffuse panbronchiolitis, BOOP–COP, granulomatous bronchiolitis (Crohn's disease), bullae and the most common of all, bronchiectasis [1,134,136]. Colectomy appears an important risk factor for the appearance or deterioration of the airways manifestations in inflammatory bowel disease. This, as well as the frequency of airways involvement, in inflammatory bowel disease might relate to several factors, such as the common ancestry of the bowel and the bronchial tree from the primitive foregut and common antigenic reminiscence, the fact that gut contains mucous-associated lymphoid tissue and the lung may develop BALT under chronic antigenic stimulation that play a cardinal role in host mucosal defense, and finally to the fact that both contain an extensive apparatus of goblet cells and submucoid exocrine glands as part of their luminal structure. Management strategies relate to the specific airway manifestation.

### BOOP–COP

BOOP, as originally described by Epler *et al.*, is an inflammatory lung lesion "characterized by polypoid connective tissue masses (Masson bodies or Bourgeons conjunctifs) composed of myxoid fibroblastic tissue, filling the lumens of terminal and respiratory bronchioles and extending in a continuous fashion into alveolar ducts and alveoli, representing an organizing pneumonia" [26,137]. The above definition emphasizes the intrabronchiolar nature of the disease, secondarily involving the alveolar-acinar structures. Actually, the most recent guidelines on ILDs consider BOOP as a primary alveolar-acinar rather than an airway process, secondarily overfilling small airways, preferring the term COP and include it among the ILDs [87,138]. Whatever the preference, BOOP and COP are both pathological descriptions that have become used as clinical diagnosis with a wide etiological spectrum. However, both the above descriptions emphasize the intraluminal (intrabronchiolar or intra-alveolar) nature of the disease and the absence of bronchiolar wall and/or acinar alveolar interstitial tissue involvement should lead us to consider BOOP–COP on its own as an alveolar space occupying inflammatory–fibrosing lesion – that is, 'immunologically mediated pneumonia'.

### Expert commentary

Bronchiolitis, an inflammatory–fibrosing condition of the intralobular conducting and transitional airways mainly, is a common process in a myriad of clinical conditions. This review advances a unifying definition of all-cause bronchiolitis and a comprehensive etiological classification. Secondary bronchiolitis participates (and occasionally predominates) in disease process of the rest of the airways and/or the surrounding lobular structures in the setting of several already defined clinical entities, mostly of known etiology, and occurs commonly. Primary or idiopathic bronchiolitis dominates and characterizes distinct clinical entities, all of unknown etiology, and occurs rarely. Acute bronchiolitis, though potentially life threatening, usually regresses. Any-cause chronic bronchiolitis contributes to morbidity and/or mortality if it persists and/or progresses to diffuse airway narrowing and distortion or complete obliteration. Bronchiolectasis–bronchiectasis also may ensue. Management depends on the specific clinical setting.

### Five-year view

Bronchiolitis is encountered in many of the respiratory diseases; thus, the future developments depend on the new knowledge regarding the etiology and management of the underlying disorders. However, emerging data regarding the immunomodulatory and anti-inflammatory potential of macrolides suggest that macrolides are helpful in treating bronchiolitis in bronchiectasis-bronchiolectasis, COPD, BOOP–COP, BOS and diffuse panbronchiolitis. With the exception of diffuse panbronchiolitis,

where macrolides already are the treatment of choice, in the next few years, researchers should validate these agents as a therapeutic option. Moreover, exploration of new therapies is urgently needed for the most severe form of bronchiolitis, the constrictive bronchiolitis obliterans, either idiopathic or secondary that presents great morbidity and mortality and no effective treatment up to now.

## Key issues

- Bronchioles are the segments of the conductive portion of the airways that, in contrast to the bronchi, lack cartilage and submucosal glands.
- Bronchiolitis, an inflammatory–fibrosing condition of the intralobular conducting and transitional airways mainly, is a common process in a myriad of clinical conditions.
- In such conditions, bronchioles, the physiologically 'silent zone' of the lungs, truly become a 'combat zone'.
- Secondary bronchiolitis participates (occasionally predominates) in the disease process of the rest of the airways and/or the surrounding lobular structures in the setting of several already defined clinical entities, mostly of known etiology, and occurs commonly. Primary or idiopathic bronchiolitis dominates and characterizes distinct clinical entities, all of unknown etiology, and occurs rarely.
- Although international consensus on bronchiolar disorders is lacking, this review proposes a unifying definition of all-cause bronchiolitis, and since imaging and histopathological features overlap among several of the above conditions, a comprehensive etiological classification is advanced.
- Acute bronchiolitis, though potentially life threatening, usually regresses. Any-cause chronic bronchiolitis contributes to morbidity and/or mortality if it persists and/or progresses to diffuse airway narrowing and distortion or complete obliteration.
- Bronchiolitis in specific settings may lead to bronchiolectasis and mucus stasis ending up in diffuse or localized bronchiectasis.
- Management depends on the specific clinical setting.

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