



REVIEW

Small airways diseases, excluding asthma and COPD: an overview

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ABSTRACT: This review is the summary of a workshop on small airways disease, which took place in Porquerolles, France in November 2011. The purpose of this workshop was to review the evidence on small airways (bronchiolar) involvement under various pathophysiological circumstances, excluding asthma and chronic obstructive pulmonary disease. Histopathological patterns associated with small airways disease were reviewed, including cellular and obliterative bronchiolitis. Many pathophysiological conditions have been associated with small airways disease including airway infections, connective tissue diseases and inflammatory bowel diseases, bone marrow and lung transplantation, common variable immunodeficiency disorders, diffuse panbronchiolitis, and diseases related to environmental exposures to pollutants, allergens and drugs. Pathogenesis, clinical presentation, a computed tomography scan and pulmonary function test findings are reviewed, and therapeutic options are described with the objective of providing an integrative approach to these disorders.

KEYWORDS: Airway pathology, connective tissue disease, constrictive bronchiolitis, drug-induced lung disease, follicular bronchiolitis, immune deficiency

The present article is a summary of a workshop on small airways disease, which took place in Porquerolles, France, in November 2011. Data reviewed during the workshop were updated with articles published in 2012. The purpose of this workshop was to review the evidence on small airways (bronchiolar) involvement under various pathophysiological circumstances, excluding asthma and chronic obstructive pulmonary disease, which have been the subject of previous publications [1–3]. Cystic fibrosis (which is also characterised by both small and large airways involvement [4, 5]) is not discussed in the present article. Histopathological patterns associated with small airways disease were reviewed, including cellular and obliterative bronchiolitis. Many pathophysiological conditions have been associated with small airways disease and not all conditions can be discussed in a single review article. We chose to focus on the major causes of small airways disease including airway infections, connective tissue diseases and inflammatory bowel diseases,

bone marrow and lung transplantation, immune deficiencies, diffuse panbronchiolitis, and diseases related to environmental exposures to pollutants, allergens and drugs. Our objective was to provide an integrative approach to these disorders by describing clinical presentation, computed tomography (CT) scan and pulmonary function test findings, and therapeutic options.

OVERVIEW OF SMALL AIRWAYS DISEASE

Small airways are usually defined as non-cartilaginous airways with an internal diameter <2 mm [3]. These airways are located from approximately the eighth generation of airways down to the terminal bronchioles (the smallest airways without alveoli) and respiratory bronchioles, which open into the gas-exchange apparatus (the alveoli). In normal lungs, small airways contribute only a little to total airway resistance [6], and it has been estimated that obstruction of 75% of all small airways is required before changes can be detected by routine pulmonary function tests (*e.g.* forced expiratory volume in

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1 s (FEV₁) [7]. Small airways are not easily visualised by imaging techniques and their histopathological analysis is best analysed in surgical lung biopsies because bronchoscopic transbronchial biopsies usually contain only a few small airways. The difficulties of sampling these airways in human subjects are responsible for the limited recognition of the important pathophysiological roles of small airways, which have been called the “silent zone”. Small airways appear particularly vulnerable because many particles and infectious agents may be deposited there and because their narrow lumen makes them more susceptible to complete obstruction than larger airways. These considerations explain why: 1) small airways involvement occurs in many diseases either isolated or in association with abnormalities in large airways and alveoli; and 2) small airways represent the major site of airflow limitation in most airways diseases [6].

Small airways disease (bronchiolitis) corresponds to a relatively limited number of elementary lesions. A classification of bronchiolitis has been proposed based on aetiology and histopathological appearance (table 1) [8]. However, this classification was largely based on the results of histopathological examination, which requires bronchoscopic or surgical biopsy that cannot be performed in all patients. Improvement in CT imaging has led to the proposal of a noninvasive diagnostic algorithm that may obviate the requirement for biopsy in some patients [9]. Although these classifications or algorithm are helpful to physicians, no single classification can fully cover the spectrum of possible causes associated with small airways disease. The diagnosis of small airways disease has to rely on integration of multiple data including clinical context and medical history, CT scan pattern and pulmonary function tests. In selected cases, histological findings will improve diagnostic accuracy, but bronchoscopic or surgical lung biopsy is not always possible or necessary. Finally, response to therapy may provide additional information, e.g.

prolonged macrolide therapy may induce dramatic improvement in subjects with diffuse panbronchiolitis.

Pathology of small airways disease

The pathology of small airways disease has been reviewed previously [8, 10–12] and, therefore, will not be extensively discussed here. Histopathological analysis of small airways disease usually requires surgical lung biopsy that allows examination of multiple small airways, whereas transbronchial biopsy only samples small numbers of airways. A limited number of elementary lesions are described in diseases associated with small airways involvement (fig. 1).

Cellular bronchiolitis is characterised by the recruitment of inflammatory cells in the small airways wall. In some cases, cellular infiltrate may show a specific organisation (e.g. granulomas or lymphoid follicles), leading to specific denominations (e.g. granulomatous bronchiolitis and follicular bronchiolitis). Granulomatous bronchiolitis is most frequently associated with tuberculosis or infection with nontuberculous mycobacteria, but can also be observed in sarcoidosis or hypersensitivity pneumonitis. Follicular bronchiolitis is characterised by the presence of lymphoid follicles (i.e. tertiary lymphoid structures containing B- and T-lymphocytes and dendritic cells with a specific organisation). Although follicular bronchiolitis has been particularly associated with Sjögren’s disease (see later section) [13], it may be observed in other diseases, including common variable immunodeficiency disorder (CVID) [14] and hypersensitivity pneumonitis, and has sometimes been described in the context of bacterial infection (e.g. *Legionella pneumophila*) [15]. Hypertrophic or confluent lymphoid follicles may result in compression of the small airways, leading to a reduction in their cross-sectional area.

The term “bronchiolitis obliterans” has been previously used for describing a wide range of histopathological lesions resulting in small airways lumen narrowing, and is still used for describing the clinical syndrome characterised by progressive and poorly reversible airflow limitation under some circumstances (e.g. lung transplantation). Histopathological use of the term bronchiolitis obliterans appears limited to a form of proliferative bronchiolitis, characterised by the presence of fibro-inflammatory polyps obstructing the small airways lumen. These lesions are often associated with endoalveolar fibro-inflammatory polyps, which are characteristic of organising pneumonia [8]. By contrast, obliterative (also called constrictive) bronchiolitis is characterised by narrowing of small airways related to patchy peribronchiolar fibrosis, which surrounds rather than fills the lumen [8].

Other lesions may be associated with small airways disease, but have been suggested to be consequences rather than causes of the disease. Mucoïd impaction results from mucous plugging in small airways related to goblet cell hyperplasia [16]. Peribronchiolar metaplasia is a common histological finding in various interstitial disorders and sometimes occurs as an isolated finding [17]. Formation of cysts (thin-walled cystic airspace) has been described in various diseases (e.g. Sjögren’s syndrome and hypersensitivity pneumonitis) and was suggested to be a consequence of small airways obstruction [18].

Importantly, various elementary lesions may coexist in a single patient but the pathological classification does not always

TABLE 1 Histological classification of bronchiolar disorders

Primary bronchiolar disorders

- Constrictive bronchiolitis (obliterative bronchiolitis and bronchiolitis obliterans)
- Acute bronchiolitis
- Diffuse panbronchiolitis
- Respiratory bronchiolitis (smoker’s bronchiolitis)
- Mineral dust airway disease
- Follicular bronchiolitis
- Other primary bronchiolar disorders, e.g. diffuse aspiration bronchiolitis and lymphocytic bronchiolitis

Interstitial lung disease with a prominent bronchiolar involvement

- Hypersensitivity pneumonitis
- Respiratory bronchiolitis-associated interstitial lung disease
- Cryptogenic organising pneumonia
- Other interstitial lung disease (pulmonary Langherans’ cell histiocytosis, sarcoidosis and bronchiolocentric interstitial pneumonia)

Bronchiolar involvement in diseases also involving large airways

- Chronic obstructive pulmonary disease
- Bronchiectasis, including cystic fibrosis
- Asthma

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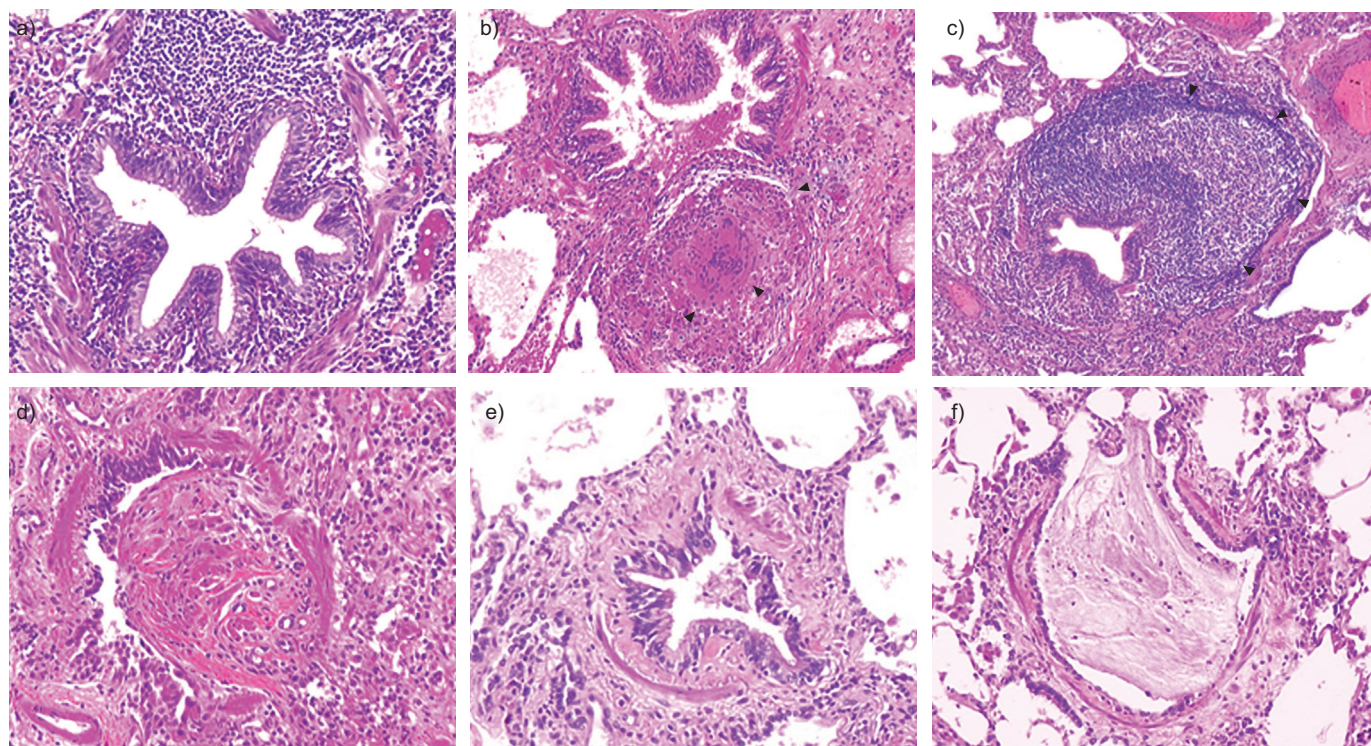


FIGURE 1. Representative photomicrographs of individual bronchiolar lesions observed in surgical lung biopsy in patients with small airways disease. a) Cellular bronchiolitis: a narrowed and contracted airway is infiltrated by numerous inflammatory cells without a specific pattern. b) Granulomatous bronchiolitis: the small airway is surrounded by an inflammatory infiltrate with a sarcoid granuloma (arrowheads), which increases the volume of the airway wall resulting in lumen narrowing. c) Follicular bronchiolitis: the small airway is surrounded by a large lymphoid follicle (arrowheads), which increases the volume of the airway wall resulting in lumen narrowing. d) Bronchiolitis obliterans is characterised by lumen obstruction with a fibro-inflammatory polyp. e) Obliterative (constrictive) bronchiolitis: the airways lumen is narrowed by subepithelial fibrosis. Although inflammatory cells and mucous exudates are present within the lumen, no fibro-inflammatory polyp is found. f) Mucous plugging: the airway lumen is obstructed by mucus exudates.

reflect clinical diagnosis. Nevertheless, histological description can be rather specific of some aetiology. Respiratory bronchiolitis, which occurs in current smokers, may be isolated or associated with interstitial lung disease (ILD). It is characterised by patchy inflammatory bronchiolitis containing pigmented macrophages with a predominant upper lobe distribution, and is eventually associated with interstitial inflammatory changes [8]. Diffuse panbronchiolitis also has characteristic features.

Imaging of small airways disease

Potential interest and limitations of the various imaging techniques that can be used for the diagnosis of small airways disease have been described previously [1–3]. Volumetric CT scans with thin sections (0.75–1.25 mm) allow multiplanar coronal or sagittal reconstructions with maximum intensity projection (MIP) and minimum intensity projection (minIP) images, and is the preferred imaging technique in subjects suspected of small airways disease [9]. Inspiratory and expiratory acquisitions are routinely obtained for assessing small airways using qualitative analysis. To date, quantitative analysis based on measurements of voxel attenuation values has only been used for research purposes. Novel voxel-wise image analysis techniques (*e.g.* parametric response map) are currently being developed and may provide improved assessment of small airways disease in the near future [19].

The spatial resolution on a CT scan is ~ 0.6 – 1 mm, which allows direct assessment of medium-sized airways (diameter 2–2.5 mm), but not of smaller airways. Thus, normal bronchioles are not visible on CT scans. Small airways disease may show direct or indirect signs on a CT scan [20]. Direct signs of small airways disease include ill-defined centrilobular nodules and well-defined centrilobular branching nodules, also called tree-in-bud opacities, which may be best seen using MIP. Indirect signs of small airways disease include a mosaic pattern of attenuation (on inspiratory CT scan) and air trapping (on expiratory CT scan and best seen using minIP). Representative CT scan images are presented in figure 2. Because centrilobular nodules and tree-in-bud opacities have been mostly associated with cellular bronchiolitis, whereas mosaic pattern of attenuation and trapping have been mostly associated with obliterative (constrictive) bronchiolitis, DEVAKONDA *et al.* [9] have recently proposed a diagnostic algorithm based on clinical context and CT findings. The authors proposed that tree-in-bud opacities suggest infectious aetiology, whereas ill-defined centrilobular nodules suggest respiratory bronchiolitis when localised in upper lobes in smokers and hypersensitivity pneumonitis when more diffuse [9]. The authors further proposed that mosaic pattern of attenuation and air trapping are suggesting of constrictive/obliterative bronchiolitis [9]. This proposal may be useful considering that most patients with suspected small airways

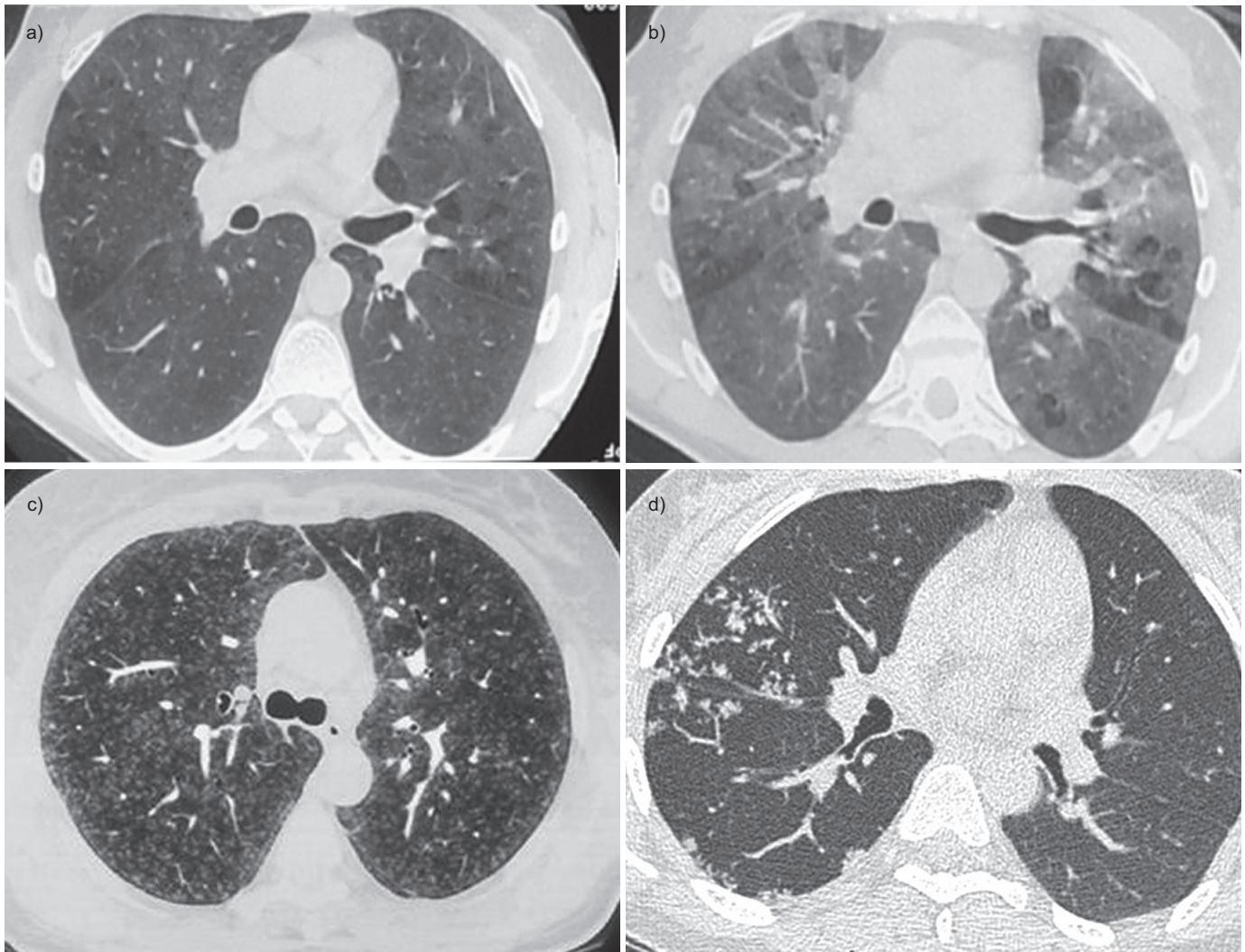


FIGURE 2. Representative images of computed tomography (CT) scans in patients with small airways disease. a) An inspiratory CT scan in a patient with hypersensitivity pneumonitis showing mosaic pattern of attenuation. b) Expiratory CT scan in the same patient showing air trapping that is characteristic of small airways disease. c) Ill-defined centrilobular nodules in a patient with farmer's lung (personal communication; J.C. Dalphin). d) Localised micronodules branching with bronchovascular structures (tree-in-bud pattern) related to tuberculosis in a patient with rheumatoid arthritis receiving treatment with anti-tumour necrosis factor- α . Reproduced from [21] with permission from the publisher.

disease will not have surgical lung biopsy, but this algorithm has not yet been prospectively validated.

SPECIFIC CAUSES OF SMALL AIRWAYS DISEASES

Infection

Post-infectious bronchiolitis is characterised by persistent inflammatory infiltrate and fibrotic lesions of small airways following a pulmonary infection and leads to airflow obstruction. It represents a rare cause of chronic airflow limitation. Because obstruction in a large number of small airways may occur before airflow limitation can be detected using conventional pulmonary function tests [22], post-infectious bronchiolitis is probably underestimated when damage to small airways affects localised areas of the lungs. Clinical features differ between children and adults. Adenovirus (especially serotypes 3, 7 and 21, which are more virulent [23, 24]) is an infectious agent frequently involved in children [25, 26]. Other infectious agents responsible for post-infectious bronchiolitis

in children include viruses (*e.g.* measles and influenza) and intracellular bacteria (*e.g.* *Mycoplasma pneumoniae*) [27–29]. The prospective study by COLOM *et al.* [30] indicates that adenovirus infection is by far the most important risk factor for post-infectious bronchiolitis, especially in cases of severe acute disease requiring mechanical ventilation.

Diagnosis of post-infectious bronchiolitis in children is based on medical history, CT scans and pulmonary function tests. Clinical manifestations are nonspecific and include cough, sputum production, dyspnoea and wheezing. These manifestations typically occur a few weeks after an episode of lower airways viral infection. A CT scan may show mosaic attenuation, air trapping, bronchial thickening, bronchiectasis, atelectasis and/or mucoid impaction [31]. Swyer-James MacLeod's syndrome corresponds to unilateral small hyperlucent lung, caused by asymmetric obliterative bronchiolitis with air trapping and diminished arterial flow. Pulmonary function

tests usually show airflow limitation and hyperinflation, which are poorly reversible with bronchodilators [32, 33].

The treatment of post-infectious bronchiolitis in children is mostly symptomatic; systemic steroids do not appear efficacious after the initial stage of acute infection, when bronchiolitis is usually diagnosed. Most severe cases may result in chronic respiratory insufficiency that sometimes requires lung transplantation [27].

In adults, the frequency of small airways disease in the context of lung infection is unclear, but appears less frequent than in children. Most reports describe post-infectious bronchiolitis obliterans with organising pneumonia (BOOP), which usually recovers spontaneously or with oral steroids [34]. Nevertheless, constrictive (obliterative) bronchiolitis is also described after viral (e.g. respiratory syncytial virus) [35] or bacterial (*Legionella*, *M. pneumoniae*) infection [36, 37], and is suggested to not respond as well as BOOP to systemic steroids [38]. Localised small airways disease, usually characterised by tree-in-bud opacities on CT scans, is also described in the context of tuberculosis or infection with nontuberculous mycobacteria [9].

Connective tissue diseases

Bronchiolar complications of connective tissue diseases are less well recognised than other pulmonary complications (e.g. ILD and pleural disease) of these disorders [39]. Sjögren's syndrome [40] and rheumatoid arthritis [41] are the two most frequent connective tissue diseases, in which bronchial and bronchiolar complications are found. Small airways disease may also occur in chronic inflammatory bowel diseases [42], as well as in other connective tissue diseases (e.g. scleroderma and systemic lupus), vasculitis or sarcoidosis [43]. Because the incidence of small airways disease is by far less frequent in these latter diseases, they will not be discussed in the present article.

Bronchiolitis in connective tissue diseases belongs to bronchiolitis of unknown origin in a well-defined context. However, it should be emphasised that the diagnosis of Sjögren's syndrome or rheumatoid arthritis may not be previously established in a patient with chronic cough or bronchial hyperresponsiveness, and that these diagnoses should be considered in patients with unexplained cough. Both follicular bronchiolitis and constrictive bronchiolitis may be encountered in subjects with connective tissue diseases and may even coexist in the same patient [41, 44]. CT scan findings in Sjögren's syndrome and in rheumatoid arthritis have been the subject of many studies [44–54], and are characterised by usual signs of small airways abnormalities, including mosaic attenuation on inspiratory CT, air trapping on expiratory CT, ground-glass opacities, and centrilobular nodules eventually with tree-in-bud pattern (especially in cellular bronchiolitis) or distension (especially in constrictive bronchiolitis). CT scans may have better sensitivity than pulmonary function tests in rheumatoid arthritis [52]. Signs of infiltrative lung disease or large bronchi involvement may be associated with signs of small airways disease [55]. Pulmonary function tests usually show poorly reversible airflow limitation that may be preceded by distal airflow limitation, as suggested by reduced forced expiratory flow at 25–75% of forced vital capacity (FVC) (FEF_{25–75%}) or at 50% of FVC (FEF_{50%}) [52].

Sjögren's syndrome

Sjögren's syndrome is characterised by abnormal function and/or destruction of exocrine glands related to infiltration by T-lymphocytes. Although salivary and lacrimal glands are most frequently involved, respiratory manifestations are frequent, varying from 9% to 75% of patients, due to the inclusion of different types of patients and the use of different methods to assess respiratory disease. Most studies and case reports have focused on infiltrative pneumonia, but small airways involvement actually seems more frequent. PAPIRIS *et al.* [56] studied airway inflammation in 13 nonsmoking patients with Sjögren's syndrome using bronchial and trans-bronchial biopsies. 10 patients had infiltration of bronchi and bronchiole submucosa by lymphocytes, which were CD4+T-lymphocytes in six patients [56]. Another study described neutrophils and mast cells in the bronchi of patients with primary Sjögren's syndrome [57]. Finally, a Japanese study found no difference in cells infiltrating small airways between primary and secondary Sjögren's syndromes [58].

Small airways disease in Sjögren's disease may be isolated or associated with nonspecific interstitial pneumonia (NSIP) or lymphoid interstitial pneumonia (LIP). ITO *et al.* [51] studied radiological and pathological findings in 33 subjects with pulmonary manifestations of primary Sjögren's syndrome. In four out of 33 cases small airways involvement was predominant, and in an additional four out of 33 cases it was associated with other abnormalities. The authors concluded that 25% of patients with primary Sjögren's syndrome had small airways abnormalities [51]. The most prevalent pathological pattern in the small airways of patients with Sjögren's syndrome is follicular bronchiolitis, in which peribronchiolar lymphoid follicles may obstruct bronchiolar lumens. Sjögren's syndrome and rheumatoid arthritis are the systemic diseases that are most closely associated with follicular bronchiolitis [59]. Other pathological patterns found in Sjögren's disease include lymphocytic (cellular) bronchiolitis (in which lymphocytes infiltrate the small airways wall without forming lymphoid follicles [60]); obliterative bronchiolitis is rarely found in primary Sjögren's syndrome, but may be observed in patients with secondary Sjögren's syndrome-associated with rheumatoid arthritis [58].

Chronic cough is present in ~50% of patients with primary Sjögren's syndrome [61] and may be related to bronchitis and bronchiolitis, but also to bronchial hyperresponsiveness that occurred in 42–60% of patients in several studies [62–64]. Mechanisms underlying bronchial hyperresponsiveness in patients with primary Sjögren's syndrome probably differ from those in asthmatic patients [65], but remain unknown. Chronic sputum production and recurring sinusitis are associated with severe chronic bronchiolitis in primary Sjögren's syndrome [66].

CT scans in Sjögren's syndrome often shows abnormalities in large airways (airway wall thickening and bronchiectasis) together with indirect signs of abnormalities in small airways (centrilobular nodules and expiratory air trapping) [48, 53, 58, 67–70].

Therapeutic options and prognosis factors in Sjögren's syndrome-associated small airways disease are not well defined. Although systemic steroids have been proposed by

some authors, it does not appear efficacious in most cases [51]. Low-dose macrolides have been proposed in subjects with bronchiolitis related to rheumatoid arthritis [41] and may be proposed in Sjögren's syndrome [65]. Inhaled steroids and long-acting bronchodilators could be proposed in patients with bronchial hyperresponsiveness, although one study suggested that this approach is not very effective in Sjögren's syndrome [71]. Treatment with rituximab could represent a therapeutic option in subjects with aggressive, severe disease [72].

Rheumatoid arthritis

Large and small airways involvement is a classic feature in subjects with rheumatoid arthritis. The only identified risk factors for airways involvement in rheumatoid arthritis are mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [73, 74]. Although the pathophysiological link between airways involvement in rheumatoid arthritis and *CFTR* mutations is unclear, heterozygous mutations in the *CFTR* gene have been associated with *CFTR* dysfunction and airways disease [75]. Surprisingly, some studies have found associations of small airways disease in rheumatoid arthritis with the absence of significant smoking history [45, 50, 52], a finding that may be related to bias in retrospective studies.

Rheumatoid arthritis is considered the most frequent connective tissue disease associated with small airways disease. However, diagnostic criteria varied among studies and the choice of criteria has a major effect on epidemiological description. GEDDES *et al.* [76] reported that 32% of patients with rheumatoid arthritis had airflow limitation. TANAKA *et al.* [44] found that 17% of patients had CT scan features suggestive of bronchiolitis. In other studies, the prevalence of small airways abnormalities ranged from 8-65% [41, 45, 52, 77, 78]. PEREZ *et al.* [52] suggested that CT scans have increased sensitivity for the detection of air trapping compared with pulmonary function tests, whereas MORI *et al.* [79] showed that 30% of patients with normal findings on CT scans have a significant reduction in FEF_{25-75%}. Respiratory symptoms appeared more prevalent in subjects with small airways abnormalities [52]. It is possible that drugs, historically used for rheumatoid arthritis (*D*-penicillamine, tiopronin or chrysotherapy), promoted the development of bronchiolitis in some patients (see later section) [80, 81].

Few studies have evaluated histopathological findings in subjects with rheumatoid arthritis-associated bronchiolitis. HAYAKAWA *et al.* [41] reported 15 cases, including seven cases of constrictive bronchiolitis and eight of follicular bronchiolitis. In a French collaborative study, DEVOUASSOUX *et al.* [55] studied 25 patients with rheumatoid arthritis and severe airflow limitation: 18 patients had FEV₁/FVC <50%; two patients had residual volume (RV)/total lung capacity >140%; and five patients had both criteria. Among nine patients with lung biopsy, histopathological patterns were constrictive bronchiolitis in six patients, follicular bronchiolitis in one patient and an association of both patterns in two patients [55]. There is no evidence that follicular bronchiolitis may precede constrictive bronchiolitis; furthermore, it is likely that constrictive bronchiolitis was more prevalent in this series because lung biopsies were mostly proposed to patients with more severe disease.

Finally, cases of diffuse panbronchiolitis have been described in Japanese patients with rheumatoid arthritis [82].

In the study by DEVOUASSOUX *et al.* [55], bronchiolitis occurred 1-35 years after the diagnosis of rheumatoid arthritis in 22 out of 25 patients and was diagnosed essentially in females (n=18). Clinical manifestations of severe bronchiolitis in patients with rheumatoid arthritis included dyspnoea in all patients, chronic cough (64%) and chronic sputum production (44%) [55]. A CT scan revealed bronchial wall thickening (96%), mosaic pattern (42%), ground-glass opacities (44%) and centrilobular emphysema (56%, which was mostly found in patients with constrictive bronchiolitis) [55]. During follow-up (48±49 months), symptoms increased in 52% of patients, with respiratory infections in 60%, pneumothorax in 12% and acute respiratory failure in 48%. Chronic respiratory failure (as defined by the need of long-term oxygen therapy) occurred in 40% of patients, including four patients who died of respiratory failure [55]. In another series that evaluated 144 patients with rheumatoid arthritis and respiratory manifestations, 5-year survival rates were 36% in 57 patients with usual interstitial pneumonia, 87% in 31 patients with bronchiectasis, 94% in 16 patients with NSIP and 89% in 11 patients with bronchiolitis [83]. It is concluded that bronchiolitis is associated with poor prognosis essentially in patients with severe airflow limitation and marked hyperinflation, and that these features mostly occurred in patients with obliterative (rather than follicular) bronchiolitis.

At present, there is no validated treatment regimen in patients with severe small airways disease associated with rheumatoid arthritis. A trial of systemic steroids may be discussed, but obliterative bronchiolitis usually does not improve with steroids or other immunosuppressive drugs. Case reports suggest that etanercept [84] or low-dose macrolides [41] may show some benefit. In most severe cases, lung transplantation may be proposed [55].

Inflammatory bowel diseases

Because the lung and the gastrointestinal tract both originate from the foregut, it is not surprising that inflammatory bowel diseases (*e.g.* Crohn's disease and ulcerative colitis) could be associated with pulmonary manifestations. Although abnormalities in large airways (*e.g.* bronchiectasis) are prevalent in these diseases, bronchiolitis has also been described [85, 86]. When present, respiratory manifestations usually occur in patients already diagnosed with inflammatory bowel disease, sometimes after colectomy [87]. Pulmonary function tests are often abnormal in patients with inflammatory bowel disease, but symptoms are less prevalent and the disease is often asymptomatic [88]. In Crohn's disease, granulomatous bronchiolitis may occur and is usually associated with ILD, although a single case of isolated granulomatous bronchiolitis has been reported [42]. Severe obliterative bronchiolitis is a rare complication of ulcerative colitis [89].

Transplantation

Bronchiolitis obliterans is the most common disease affecting small airways after lung transplantation. It also occurs in patients with allogeneic (but not autogenic) haematopoietic stem cell transplantation (HSCT). Clinical manifestations of bronchiolitis obliterans after transplantation include progressive dyspnoea, eventually associated with chronic cough and

sputum production, and progressive airflow limitation that may result in respiratory failure. Bronchiolitis obliterans after lung transplantation and after allogeneic HSCT are different diseases, but share some features (table 2). Confirmation of the diagnosis of bronchiolitis obliterans requires histopathological examination. Bronchiolitis obliterans after lung transplantation is characterised by intraluminal polyps comprised of fibromyxoid granulation tissue and plaques of dense submucosal eosinophilic scar [90]. However, histopathological confirmation of bronchiolitis obliterans may be difficult to obtain because open-lung biopsy is seldom performed and transbronchial biopsy has poor sensibility for the diagnosis of bronchiolitis obliterans due to the small size of samples and the focal nature of this disease. The International Society for Heart and Lung Transplantation (ISHLT) has proposed the term bronchiolitis obliterans syndrome (BOS) for patients with clinical manifestations compatible with bronchiolitis obliterans but without histopathological confirmation [90]. By analogy, BOS is often used after allogeneic stem cell transplantation.

Bronchiolitis obliterans after lung transplantation

Bronchiolitis obliterans is the main complication after lung transplantation and is the first cause of death after the first year of transplantation [91]. The ISHLT Registry shows that at 1, 3, 5 and 10 years from transplantation, 90%, 70%, 50% and 30% of patients, respectively, have no clinical manifestations of bronchiolitis obliterans [91]. Median survival appears longer in patients with slow and delayed onset of airflow limitation after lung transplantation [92].

Two phenotypes of patients with bronchiolitis obliterans after lung transplantation have been identified, although intermediate phenotypes may exist. The first phenotype comprises patients with dyspnoea, chronic cough and purulent sputum production. Lung auscultation often reveals crackles and CT

scans show air trapping on expiration, mucoid impaction and bronchiectasis. In these patients, airway neutrophilia is often prominent and azithromycin may have a beneficial effect on lung function. The second phenotype comprises patients with isolated dyspnoea, normal auscultation and isolated air trapping on expiratory CT scans. These patients have no significant airway neutrophilia and do not respond favourably to azithromycin [93].

Incidence of BOS is not associated with the clinical characteristics of the donor and the receiver, the type of lung transplant (single *versus* double lung transplantation) or the underlying pulmonary disease leading to transplantation [94]. Acute rejection (including low-grade vascular rejection [95–97]) appears to be the main factor associated with BOS [98]. However, acute rejection is not always associated with BOS and some patients with BOS had no previous acute rejection. Development of class I or class II donor-specific anti-human leukocyte antigen (HLA) antibodies is also associated with an increased risk of BOS [99]. Cytomegalovirus (CMV) pneumonia and CMV mismatch between CMV-positive donor and CMV-negative receivers have been associated with BOS in some [100], but not all, studies [101]. Community-acquired respiratory virus infections have also been associated with BOS [102], although a recent meta-analysis did not confirm this association [103], probably due to the heterogeneity of published studies. Gastro-oesophageal reflux disease (GORD) is a risk factor for BOS and retrospective studies suggest that surgical fundoplication in the first 3 months after transplantation prevents BOS [104], and that fundoplication may improve lung function in patients with established BOS [105]. A recent prospective study has shown that fundoplication results in improved lung function at 1 year post-transplantation, as compared with medical therapy in patients with clinically significant GORD [106].

TABLE 2 Comparison of bronchiolitis obliterans (BOS) after lung transplantation and after allogeneic haematopoietic stem cell transplantation (HSCT)

	BOS after lung transplantation	BOS after allogeneic HSCT
Risk factors		
Immunology	HLA mismatch	GVH disease
Cytomegalovirus infection	Yes	Not established
Community-acquired viral infections	Suspected	Suspected
GORD	Yes	Not established
Prevalence	9% at 1 year 38% at 5 years 58% at 10 years	5.5%; 14% in patients with GVH disease
Clinical presentation		
Heterogeneous	Yes, two phenotypes	Yes
Pathology	Heterogeneous	Heterogeneous
Treatment		
Immunosuppression	Optimisation No increase	Optimisation No increase
Azithromycin	In subjects with alveolar neutrophilia	Not established
Surgical treatment of GORD	Yes	Not established
Lung (re)transplantation	In selected patients	In selected patients

GORD: gastro-oesophageal reflux disease; HLA: human leukocyte antigen; GVH: graft-versus-host.

Pathogenesis of bronchiolitis obliterans after lung transplantation remains incompletely understood. Classically, bronchiolitis obliterans has been considered as the expression of chronic lung rejection. This concept has evolved since non-immunological risk factors (see above) have been identified. It seems possible that bronchiolitis obliterans is the ultimate consequence of repeated injuries to lung allograft, related to immune and non-immune mechanisms. One hypothesis is that injury to the epithelium of small airways results in an abnormal repair characterised by recruitment of inflammatory cells and excessive fibro-proliferation. Acute cellular rejection is a risk factor for BOS and recent data also suggest that acute or chronic antibody-mediated rejection may play a role in the development of BOS [107]. Anti-HLA class I antibody binding to epithelial or endothelial cells induce cell proliferation and production of fibrogenic growth factors [108]. Graft damage related to rejection may expose cryptic antigens (e.g. α -1-tubulin, collagen I and V) and induce autoimmunity, which is associated with increased risk of BOS [107]. It is possible that such autoimmune reaction may also be triggered by primary graft dysfunction related to ischaemia-reperfusion mechanisms [109], bacterial, viral or fungal infections [110], or GORD [111]. Epithelial damage may result in an excessive T-helper (Th)17 response, inducing neutrophil recruitment. Imbalance between Th17 lymphocytes and regulatory T-cells may determine the outcome: *restitutio ad integrum* or bronchiolitis obliterans [112]. Under some circumstances, epithelial damage may induce epithelial-to-mesenchymal transition in the airways, as observed in idiopathic pulmonary fibrosis [113].

Potential treatments of BOS may be more effective at an early (inflammatory) than at a later (fibrous) stage. Thus, early detection of BOS has been a major research interest for many groups. Assessment of ventilation heterogeneity using single-breath nitrogen washout (SBNW) revealed that ventilation abnormalities 6-12 months before airflow abnormalities could be detected by spirometry in subjects with bilateral lung transplantation [114]. It has a good sensitivity and a very good negative predictive value for BOS [114]. Nitric oxide and carbon monoxide concentrations in exhaled breath have been correlated with airway neutrophilia in subjects with BOS, but their sensitivity is lower than SBNW [115]. Neutrophilia (>20%) in bronchoalveolar lavage is predictive for future BOS in stable lung transplant recipients [116]. Exhaled breath condensates, induced sputum, bronchoalveolar lavage, and CT scans have all been evaluated for early detection of BOS. However, these tools cannot be recommended at present since they have not been validated in large multicenter studies.

Prevention of BOS is a major objective after lung transplantation. Pharmacokinetic optimisation of immunosuppressive therapy *via* therapeutic drug monitoring of immunosuppressive agents is important for prevention of acute rejection [117-119]. Prevention of CMV pneumonia and community-acquired viral infection (e.g. *via* influenza vaccination) is of utmost importance. GORD must be detected and aggressively treated. Bronchoalveolar neutrophilia should be assessed, and azithromycin may be initiated in patients with increased neutrophilia [120]. A recent pilot study evaluating azithromycin- *versus* placebo-initiated therapy immediately after transplantation in 80 lung transplant recipients showed that incidence of bronchoalveolar neutrophilia and BOS were significantly

reduced by azithromycin at 2 years post-transplantation [121]. Large multicenter studies are required to confirm these promising findings. Two retrospective studies have shown that treatments with statins inhibited class II HLA expression, diminished response to alloantigens and cytotoxic T-lymphocytes, reduced growth factor synthesis, and were associated with a reduction in BOS incidence and improved survival [122, 123]. However, these data will require confirmation in randomised prospective studies.

When BOS is established, pharmacokinetic optimisation of immunosuppression may result in BOS stabilisation [124-126], but increasing the level of immunosuppression is generally unsuccessful and may be associated with increased risk of infections. Azithromycin may improve BOS in ~50% of patients, especially in those with increased airway neutrophilia [127]. Total lymphoid irradiation may reduce FEV₁ decline [128]. Lung retransplantation may be considered in some patients, although survival is lower than after the first transplantation [129].

Bronchiolitis obliterans after allogeneic HSCT

Bronchiolitis obliterans after allogeneic HSCT is usually considered as a chronic graft-*versus*-host (GVH) pulmonary manifestation [130]. As for bronchiolitis obliterans after lung transplantation, histopathological confirmation of diagnosis (which requires surgical biopsy) is rarely obtained, and BOS is suspected in patients with airflow obstruction and air trapping on CT scans, usually in the presence of extrapulmonary chronic GVH disease [130, 131]. In a recent large cohort study, the overall prevalence of BOS was 5.5% and increased to 14% in patients with chronic extrapulmonary GVH disease [132]. BOS onset occurred at a median time of 15-18 months after transplantation.

Histopathological studies show heterogeneous lesions in different patients, but also within the same patient, suggesting that lesions of different ages co-exist. Studies have found obliterative bronchiolitis or lymphocytic (cellular) bronchiolitis with abnormalities in bronchiolar epithelium [133, 134]. A recent study has suggested that lymphocytic bronchiolitis has better prognosis [134].

Several risk factors for BOS after allogeneic HSCT have been proposed in retrospective studies [132, 135-141]. The only risk factor that was consistently observed in these studies is chronic extrapulmonary GVH disease. A recent study has suggested the role of community-acquired respiratory viruses in triggering BOS [142].

Limited data exist on the pathogenesis of bronchiolitis obliterans after allogeneic HSCT. Most data come from studies performed on bronchiolitis obliterans after lung transplantation (see above) or on GVH disease. GVH disease is related to alloimmune reactions that occur in the presence of donor T-lymphocytes [143]. Results obtained in humans and in animal models of GVH disease are somewhat controversial, but T- and B-cell abnormalities occur [143, 144]. In humans with bronchiolitis obliterans after allogeneic HSCT, peribronchiolar infiltrate was composed of CD8+T-lymphocytes in one patient [145] and of B-lymphocytes in another patient [146]. Genetic variations in bactericidal/permeability-increasing protein influence the risk of BOS after allogeneic HSCT [147]. Recently, a new

murine model for bronchiolitis obliterans after allogeneic HSCT has reproduced bronchiolar abnormalities mimicking human disease [148], and may provide insights into the pathogenesis of bronchiolitis obliterans in humans.

BOS after HSCT is associated with reduced survival [132], which is poorer when BOS occurs soon after transplantation [149]. Bronchoalveolar lavage shows either lymphocytic alveolitis or neutrophilia, and is not required for diagnosis [150]. Atypical cells in bronchoalveolar lavage have been associated with chronic pulmonary GVH [151], but may only reflect epithelial injury by drugs utilised for pre-transplantation conditioning [152]. Air trapping on expiratory CT scans has been suggested as diagnostic criteria by the National Institutes of Health (NIH) consensus [130], although little data exist on its specificity in patients who have previously received many drugs with potential pulmonary toxicity.

The therapeutic approach of BOS after allogeneic HSCT is not well established. An increase in systemic immunosuppression (including oral steroids) may increase rates of severe, potentially lethal, infections and should not be advised [149]. Inhaled steroids and long-acting bronchodilators may improve lung function and pulmonary symptoms, and have very limited side-effects [153–155]. Lung transplantation may be proposed in selected patients without active chronic extra-pulmonary GVH disease [156].

Common variable immunodeficiency disorders

CVID represent a heterogeneous group of conditions characterised by a low level of circulating IgG, IgA and/or IgM, and leading to increased susceptibility to infections [157]. Although the pathophysiology of CVID is not fully understood, it seems that B-lymphocytes fail to undergo normal maturation into plasma cells (which produce the antibodies). Abnormalities in T-lymphocytes are also frequently observed in patients with CVID [157]. The prevalence of CVID is estimated as approximately one in 30 000 individuals. Clinical manifestations in patients with CVID are related to three mechanisms: 1) recurring infections related to the failure to produce sufficient antibody levels; 2) autoimmune diseases that are observed in up to 20% of patients and are probably related to immune dysregulation or to a defect in antigen clearance [94]; and 3) lymphoid hyperplasia with increased incidence of B-cell lymphoma, thymoma and solid cancer (especially stomach cancer) [158].

At the pulmonary level, recurring infections may be responsible for bronchiectasis (which is found in 4–52% of patients). Lymphoid hyperplasia and granulomatous lesions may infiltrate alveoli and bronchioles; this non-infectious complication of CVID is being called granulomatous-lymphocytic interstitial lung disease (GLILD) [14].

Follicular bronchiolitis is characteristic of small airways involvement in CVID: lymphoid follicles, containing a germinal centre with proliferating CD20+ B-lymphocytes, are found around the bronchioles and are associated with neutrophil recruitment and mucous obstruction [13, 14, 159]. Follicular bronchiolitis may be associated with other manifestations of GLILD, including LIP and granulomatous disease. LIP, which mostly contains CD3+ T-lymphocytes, has been found with a frequency of 3% in patients with CVID [160]. Granulomatous

disease is observed in 8–23% of patients with CVID, and largely mimics sarcoidosis with non-necrotising granuloma infiltrating both alveoli and airways [14, 157, 158, 161]. A recent case-control study has found that granulomatosis-associated CVID disorders have a specific clinical presentation, often characterised by crackles at auscultation, air bronchograms, halo signs and bronchiectasis on CT scans, and have worse prognosis compared to sarcoidosis [161]. Organising pneumonia has also been described in patients with CVID/GLILD [162, 163], and GLILD is often associated with autoimmune manifestations [94, 160, 164, 165].

Clinical manifestations of follicular bronchiolitis and GLILD in patients with CVIDs have been described in a cohort of 69 patients who were classified into three groups: Group 1 was composed of patients without respiratory symptoms or abnormalities on chest radiographs; Group 2 was composed of patients with respiratory symptoms but without diffuse radiographic abnormalities; and Group 3 was composed of patients with chronic respiratory symptoms and diffuse radiographic abnormalities [166]. Patients in Group 3 were divided into two subgroups on the basis of the histopathological pattern seen on lung biopsy: a subgroup that met GLILD criteria and a subgroup with all other types of ILD. The authors found that in patients with GLILD, follicular bronchiolitis, LIP and granulomatous disease often coexist and are associated with respiratory symptoms (dyspnoea, cough and, chest pain) and CT scan abnormalities (reticulo-nodular infiltrates, alveolar consolidation, ground-glass opacities and centrilobular micronodules) [166]. In some Group 2 patients, CT scan abnormalities (centrilobular nodules, tree-in-bud pattern and mosaic lung attenuation) often found in bronchiolitis were observed, suggesting that follicular bronchiolitis may exist in the absence of infiltrative lung disease [166].

Few studies have evaluated the associations between CT scan abnormalities and pulmonary function tests in patients with CVID. In a cohort of 65 patients, correlation was found between bronchial wall thickening, mucoid impaction and mosaic lung attenuation on the one hand and airway obstruction (FEV₁ and FEV₁/FVC) on the other [167]. Low diffusing capacity of the lung for carbon monoxide (DLCO) was associated with bronchial wall thickening and linear opacities. In another study of a cohort of 51 children with CVID, the authors reported correlations between air trapping on CT scans and distal airway obstruction, as measured by FEF_{25–75%} [168].

Among CVID patients, those with GLILD have worst survival. Death is often related to extrapulmonary localisations of granulomatous disease (e.g. liver cirrhosis) and to autoimmune manifestations [166]. Treatments of follicular bronchiolitis or GLILD are not well established. Although systemic steroids are often prescribed, their efficacy is inconstant. Individual case reports have suggested possible efficacy of other immunosuppressive drugs (cyclosporin A, anti-tumour necrosis factor- α) in patients with GLILD [169, 170].

Diffuse panbronchiolitis

Diffuse panbronchiolitis is a rare disorder, which has been initially described in Japan and mostly affects east Asian people, although a few cases have been described in Caucasians. Diffuse

panbronchiolitis has been the topic of recent reviews [171, 172], and will not be extensively discussed here.

Diffuse panbronchiolitis occurs in the fourth to sixth decade of life and is clinically characterised by recurrent sinus and airway infection, associated with the rapid development of bronchiolitis and bronchiectasis. CT scan abnormalities include centrilobular nodules that may be connected to distal branching bronchovascular structures (tree-in-bud pattern) and may be associated with cyst and bronchiectasis [173]. The disease is usually diffuse, affecting both upper and lower lobes. Airflow limitation and hyperinflation may worsen rapidly, leading to respiratory failure and death.

Histopathological examination indicates that the disease is focused on respiratory bronchioles, where it affects all layers of the bronchial wall. The inflammatory infiltrate is composed of neutrophils, CD8 T-lymphocytes and foamy macrophages. The airway epithelium may be damaged and shows extensive goblet cell hyperplasia with secretion of MUC5AC and MUC5B mucins [174, 175]. Genetic predisposition related to specific HLA genotypes or polymorphisms in MUC5B mucin have been suggested [176].

Prolonged treatment with low-dose macrolides has been shown to often result in dramatic improvement in some patients and sometimes in complete recovery [177]. In a recent study of 24 patients with diffuse panbronchiolitis treated for 3 months with erythromycin, decreased air trapping on CT scan correlated with an improvement of centrilobular nodules, suggesting an effect of therapy on obstructive lesions in small airways [178]. In a recent study, the authors performed repeated multiple nitrogen washout tests to evaluate acinar (S_{acin}) and conductive (S_{cond}) ventilation heterogeneity in a single patient with diffuse panbronchiolitis treated with azithromycin [179]. The authors found that after 5 months of azithromycin treatment S_{cond} fell within the normal limit, whereas S_{acin} was still abnormal after 16 months of treatment, suggesting that macrolides cannot reverse the acinar component of ventilation heterogeneity in diffuse panbronchiolitis [179].

Drug-induced small airways disease

Lung or airway abnormalities may occur during treatments with many different drugs (www.pneumotox.com) and lead to multiple patterns. Here, we will limit the discussion to the very limited number of drugs that have been associated with bronchiolitis, excluding organising pneumonia (sometimes called BOOP) [180, 181] and drug-induced bronchospasm [182]. Drugs associated with bronchiolitis include some treatments of rheumatoid arthritis (*D*-penicillamine, chrysotherapy and tiopronin) and busulfan-based conditioning for allogeneic haematopoietic cell transplantation. These medications were, or are still, prescribed for conditions already responsible for bronchiolitis (see above), which leads to difficulties in establishing a firm causal relationship.

The role of *D*-penicillamine in the induction of bronchiolitis has been suspected since 1976 [183]. Most of the descriptions of *D*-penicillamine-associated bronchiolitis were reported in the 1980s [184] but not since, which probably reflects the currently limited use of the drug. DEVOUASSOUX *et al.* [55] reported 25 cases of severe obliterative bronchiolitis in rheumatoid arthritis and found that 12 patients had previously received

D-penicillamine, one patient had received tiopronin and 10 patients had received chrysotherapy. Patients who had received *D*-penicillamine had significantly lower FEV₁ than those who did not (800 ± 320 mL *versus* 1240 ± 320 mL, respectively, $p < 0.01$). Histopathological examination in patients who had received *D*-penicillamine found follicular or constrictive bronchiolitis, sometimes co-existing in the same patient [55]. Onset of symptoms occurred at a mean 6-7 months after starting *D*-penicillamine, which may be faster than in patients with rheumatoid arthritis who did not receive *D*-penicillamine [185]. A case of obliterative bronchiolitis was also reported in a patient with localised scleroderma treated with *D*-penicillamine [186].

Chrysotherapy has also been suspected to induce bronchiolitis. TOMIOKA and KING [81] have analysed 140 published cases of gold-induced pulmonary disease; gold was prescribed in 80% of cases for rheumatoid arthritis. The authors found four cases of bronchiolitis. A case of constrictive bronchiolitis obliterans was reported 4 months after initiating intra-muscular chrysotherapy for psoriatic arthritis [187]. Fatal bronchiolitis was also reported 6 months after initiating chrysotherapy in a patient with juvenile rheumatoid arthritis [188]. Tiopronin, another drug sometimes utilised in the treatment of rheumatoid arthritis, has been associated with bronchiolitis in a very limited number of cases [55, 189].

Busulfan is an alkylating antineoplastic agent, which has long been associated with drug-induced interstitial pneumonia [190]. Busulfan, together with cyclophosphamide and/or total body irradiation, has been utilised for destroying the recipient's immune system before allogeneic bone marrow transplantation. In a prospective study, RINGDEN *et al.* [191] found that bronchiolitis with airflow limitation occurred in 26% of patients who received a busulfan-based regimen *versus* 5% of patients who received cyclophosphamide-total body irradiation. In a retrospective analysis of a registry of patients receiving allogeneic HSCT for leukaemia, the authors found that previous treatment with busulfan was associated with an increased risk for bronchiolitis obliterans (HR 2.24, 95% CI 1.39-3.60, $p < 0.009$ [192]). A recent retrospective study of 1145 patients with allogeneic haematopoietic cell transplantation found bronchiolitis obliterans in 5.5% of patients and reported no association with busulfan [132].

Sauropus androgynus is a shrub grown in some tropical regions and is used as a leaf vegetable in various countries (*e.g.* south-east China, Indonesia, Malaysia and Vietnam). In 1996, an outbreak of bronchiolitis obliterans associated with the consumption of *Sauropus androgynus* was reported in 278 patients in Taiwan [193]. The clinical presentation associated progressive dyspnoea and persistent cough with ground-glass opacities and bronchiectasis on CT scan examination and irreversible airflow limitation. Patients had absorbed uncooked *Sauropus androgynus* juice or dry powder (usually used for alleged anorexigen properties) for a mean period of 6 months. Response to prednisolone was very limited; nine patients died and eight patients underwent lung transplantation. A dose-response relationship was established between the consumption of *Sauropus androgynus* and irreversible obstructive ventilatory defect, further reinforcing causality [194]. Five additional cases have been subsequently reported in Japan

[195]. Because papaverine is a major component of *Sauropus androgynus*, it has been suspected to play a role in the development of bronchiolitis obliterans under these circumstances and repeated intratracheal instillation of papaverine indeed mimicked human bronchiolitis obliterans in rats [196]. However, papaverine is widely used for its antispasmodic properties and no case of papaverine-associated bronchiolitis has been reported, making the relevance of these animal findings questionable.

A single report suggests an association of topotecan, a topoisomerase I inhibitor used in the treatment of ovarian carcinoma and nonsmall cell lung cancer, with bronchiolitis obliterans [197]. In a series of nine cases describing respiratory complications associated with dasatinib, one patient had received dasatinib therapy after occurrence of bronchiolitis obliterans ascribed to imatinib [198]. Repeated aspiration of particulate matter (e.g. talc, cellulose, crospovidone and sodium polystyrene sulfonate), for medical purposes [199], or psyllium (a laxative compound) [200] may also cause bronchiolitis.

Environmental or occupational exposure

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis is one of the most frequent causes of small airways diseases. It is usually due to the inhalation of organic dust (e.g. mouldy hay or straw) but can also occur with the inhalation of chemical compounds (e.g. isocyanates) [201, 202]. Pathologically, hypersensitivity pneumonitis is characterised by an inflammatory process with granulomatous infiltration of the lung interstitium and small airways. Although hypersensitivity pneumonitis is often considered an interstitial lung disease, small airways disease is constant and sometimes predominates [203, 204].

Farmer's lung (related to exposure to hay or straw) and pigeon breeder's disease (related to exposure to bird dejections) are among the most frequent forms of hypersensitivity pneumonitis, but novel environmental exposures can also be involved. For example, exposure to household moulds (related to increasing use of air conditioning and humidifiers) has been associated with hypersensitivity pneumonitis [205]. Exposure to *Mycobacterium avium intracellulare* in hot tubs (hot tub lung) [206–209] or to *Mycobacterium immunogenum* in metalworking fluids used in the industrial sector (machine operator's lung) [210] have also been associated with hypersensitivity pneumonitis.

A number of diagnostic criteria for hypersensitivity pneumonitis have been described. Six criteria may be used to suspect hypersensitivity pneumonitis and avoid lung biopsy: 1) evidence of exposure to appropriate antigen; 2) detection of serum antibody to this antigen; 3) recurrence of symptoms (fever, chills, cough, dyspnoea, etc.); 4) often occurring within 4–8 h after antigen exposure; 5) presence of inspiratory crackles; and 6) weight loss [211]. In Type 1 (acute) hypersensitivity pneumonitis, the onset of symptoms (fever and chills) occurs a few hours after antigen exposure, whereas Type 2 hypersensitivity pneumonitis is usually related to chronic antigen exposure and characterised by digital clubbing and pulmonary function test abnormalities (with restrictive and/or obstructive pattern, hypoxaemia and low DLCO), and may evolve into pulmonary fibrosis and/or emphysema despite antigen avoidance [212].

Structural abnormalities in hypersensitivity pneumonitis have been described in subjects with farmer's lung or pigeon breeder's disease [213–216]. In acute or subacute disease lung inflammation is characterised by cellular infiltrates containing CD8+T-lymphocytes, neutrophils, macrophages, plasmacytes and mast cells. This cellular infiltrate may form granulomas surrounding and/or compressing bronchioles, eventually leading to bronchial obstruction. Giant cells are often present, even in the absence of granuloma. Bronchiolitis obliterans with endobronchial proliferation may be found in 10–50% of cases [217]. In chronic disease, peribronchiolar fibrosis leading to obliterative bronchiolitis may occur, and is generally associated with pulmonary fibrosis.

Chest radiographs may be normal in 20% of cases of hypersensitivity pneumonitis, underlining the importance of CT scans [218]. CT scan abnormalities may reflect cellular infiltration with ground-glass opacities and ill-defined centrilobular nodules corresponding to granulomatous lesions [204, 219]. They may also reflect ventilation abnormalities related to bronchiolitis with mosaic attenuation on inspiration and air trapping on expiration. Emphysema and fibrosis mimicking usual interstitial pneumonia may be found in chronic disease [220, 221].

Clinical manifestations of hypersensitivity pneumonitis include chronic cough and sputum production in up to 50% of patients [222–225]. Nonspecific bronchial hyperresponsiveness [226, 227] and wheezing may also be prevalent in subjects with recent hypersensitivity pneumonitis, especially in dairy farmers [228, 229].

Pulmonary function tests in acute hypersensitivity pneumonitis usually show a restrictive pattern with low DLCO [201]. In subacute hypersensitivity pneumonitis, RV may be normal or even increased and correlated with air trapping on CT scans [219]. Airflow limitation (defined by an FEV₁/FVC ratio <70%) occurred in 10–17% of patients with farmer's lung or pigeon breeder's disease at diagnosis [223, 225, 228]. Following acute or subacute hypersensitivity pneumonitis, 30–65% of patients remain symptomatic and ~30% develop chronic respiratory failure. Long-term longitudinal cohorts indicate that emphysema with airflow limitation often occurs during follow-up [221, 230, 231], especially in farmer's lung and in hypersensitivity pneumonitis related to intermittent allergen exposure. Chronic exposure to low concentrations of antigen (e.g. pigeon's breeder lung) usually leads to pulmonary fibrosis.

Bronchiolitis related to other environmental exposures

Smoking exposure may cause histopathological lesions in large airways and alveoli, but also in small airways. Bronchiolitis induced by tobacco-smoke exposure, also called respiratory bronchiolitis, may be isolated or associated with ILD and is usually classified among interstitial pneumonitis. Respiratory bronchiolitis is usually asymptomatic, but CT scans may show ill-defined centrilobular nodules. When respiratory bronchiolitis is associated with interstitial pneumonia, CT scans usually show ground-glass opacities and centrilobular lobules with upper lobe predominance. Diagnosis is easily obtained in a smoking patient due to bronchoalveolar lavage, which shows very high cellularity (>10⁶ cells·mL⁻¹) comprised of macrophages. The prognosis is usually related to other consequences of tobacco-smoke exposure including respiratory insufficiency.

Although asbestos has been suspected to induce bronchiolitis, a recent study did not confirm this hypothesis [232]. Bronchiolitis induced by chronic inhalation of mineral particles or acute inhalation of toxic gas (such as NO₂) are other examples of damage to small airways due to environmental exposures. Pathophysiological mechanisms are probably different from hypersensitivity pneumonitis and damage to bronchioles is exclusive or predominant. Finally, complex lung exposure observed in some rare cases (such as in the World Trade Center disaster [233] or during war [234]) may lead to less well-characterised patterns of small airway diseases.

CONCLUSION

Located at a transitional zone between larger airways and lung interstitium, small airways may be affected in a wide variety of pathophysiological conditions. Although major progress has been achieved in the recognition of small airways disease, diagnosis still remains difficult in 2013. Noninvasive methods for the diagnosis have been greatly improved by progress in CT scan imaging, and novel image analysis software may even increase our ability to monitor small airways disease without the requirement of lung biopsy [19]. Environmental and drug exposures are changing rapidly and these changes may lead to the occurrence of new conditions associated with novel drugs or environmental exposures or to improvement of existing disease. Treatment of small airways diseases is not well established due to the wide variety of causal factors and their often late diagnosis. Better and earlier identification of small airways diseases should improve the possibilities to propose earlier treatment intervention. For example, very little information is currently available on potential effects on small airways disease of targeted therapies used in connective tissue diseases. Collaborative research will be required to improve knowledge in these relatively rare diseases.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at err.ersjournals.com

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We dedicate this manuscript to honour the legacy of our dear co-author and friend Isabelle Tillie-Leblond (1965–2013), for her outstanding contribution to respiratory disease care and research, and her unconditional friendship.

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