Review

Primary bronchiolar disorders: diagnosis and treatment

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SUMMARY. Bronchiolitis is a generic term applied to a variety of inflammatory diseases that affect the bronchioles, sparing a considerable portion of the other parenchymal structures, in which both inflammatory cells and mesenchymal tissue are present. Bronchiolitis occurs in a variety of clinical settings and may be associated with large airway disease and parenchymal disease. The symptoms and signs of bronchiolitis are nonspecific and polymorphous. The course is usually chronic, but it may be acute or subacute. The advent of high resolution computerized tomography scan (HRCT) has enabled the identification of more specific patterns that correlate with the involvement of the small airways, and it is clinically useful for confirmation of suspected bronchiolar lesions. Recently, improvement has been noted in the prognosis and clinical outcome of the disease mainly as a result of the application of macrolide treatment. Currently many clinical trials are in progress aimed at the identification of the most appropriate treatment for each specific type of bronchiolitis. ***Pneumon 2010, 23(1):64-79.***

INTRODUCTION

Bronchiolitis is a generic term applied to a variety of inflammatory diseases that affect the bronchioles, the small airways (i.e., less than 2 mm in diameter) that do not contain cartilage in their walls. Bronchiolitis may be defined as a process centred in and around the membranous and/or respiratory bronchioles, in which inflammatory cells and mesenchymal tissue are both present, but sparing a considerable portion of the other parenchymal structures[1]. Bronchiolitis is common and occurs in a variety of clinical settings[2,3] (e.g., infections, connective tissue diseases, inhalational injuries, cigarette smoking and drug reactions, and following stem cell and solid organ transplantation), and in association with large airway disease[4,5] (e.g., bronchiectasis) and parenchymal disease (e.g., hypersensitivity pneumonitis)[6]. Although bronchiolitis is commonly seen in association with organizing pneumonia, the main component in that case is parenchymal

disease and therefore it will not be presented here. This is a review of the approach to the diagnosis and treatment of primary bronchiolar disorders.

DIAGNOSTIC APPROACH

A. Anatomic and physiological features of the bronchioles

In contrast to the bronchi, the bronchioles normally do not contain cartilage, submucosal glands, or goblet cells. Cilia are more sparsely distributed in bronchiolar epithelial cells than in the bronchi, and the bronchiolar smooth muscle is not under vagal control. Repeated branching creates a large number of bronchioles arranged in parallel, resulting in a large total cross-sectional area, with the result that bronchioles normally contribute little to total airflow resistance[1] (Figure 1). Because their walls are not rigid, the dimensions of the bronchioles change with the lung volume. They narrow markedly at low lung volumes, and their contribution to resistance increases at the level of residual volume (RV). Local peripheral narrowing may decrease the ventilation of a diseased area, leading to hypoxaemia, although this narrowing may not produce wheezing or striking increases in the total work of breathing. For these reasons, pathological narrowing of the peripheral airways is difficult to detect, and these airways may be considered a "silent zone" of the lung[7]. Despite repeated efforts to design tests for identifying obstruction in the peripheral airways, no method so far has been entirely successful.

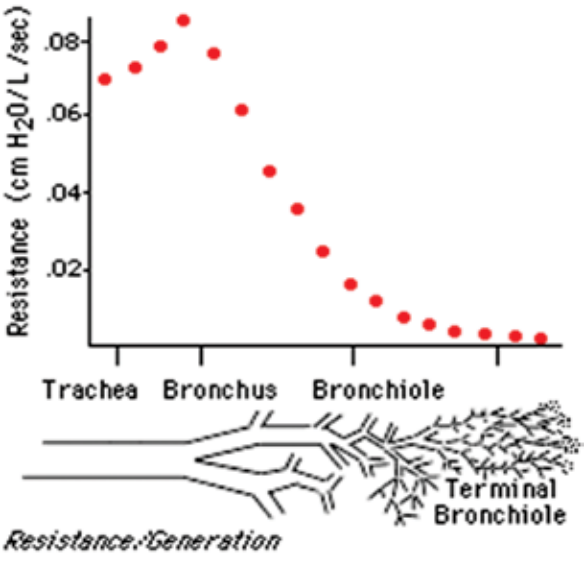


FIGURE 1. Location of the chief site of airway resistance. Note that the intermediate-sized bronchi contribute most of the resistance, in contrast to the very small airways, due to their prodigious number and their parallel arrangement.

B. Classification of bronchiolitis

Bronchiolitis can be classified in several ways, according to its proven or presumed aetiology or to the pulmonary or systemic diseases with which it is often associated[6,8], or based on its histological features[9,10]. Although an aetiological classification is useful for reminding the physician of when to suspect the presence of bronchiolitis, a scheme based on the histological characteristics is more valuable for two reasons: (a) the histological pattern of bronchiolitis generally shows better correlation with the clinical and radiological manifestations of the disease than do the various aetiological factors, and (b) the histological classification shows better correlation with the natural history of the disease and its response to treatment. However, the histological findings are relatively nonspecific and must therefore be interpreted in the context of the clinical and radiological findings[10] (Table 1). Some of the histological

TABLE 1. Classification of bronchiolar disorders

Primary bronchiolar disorders
- constrictive (obliterative) bronchiolitis
- acute bronchiolitis
- diffuse panbronchiolitis
- respiratory bronchiolitis
- follicular bronchiolitis
- mineral dust airway disease
- other primary bronchiolar disorders (eg., diffuse aspiration bronchiolitis, lymphocytic bronchiolitis)

Interstitial lung diseases with a prominent bronchiolar involvement
- hypersensitivity pneumonitis
- respiratory bronchiolitis-associated interstitial lung disease/ desquamative interstitial pneumonia
- cryptogenic organizing pneumonia (proliferative bronchiolitis)
- other interstitial diseases (pulmonary Langerhans' cell histiocytosis, sarcoidosis, bronchiolocentric interstitial pneumonia)

Bronchiolar involvement in large airway diseases
- chronic bronchitis – chronic obstructive pulmonary disease (COPD)
- bronchiectasis
- asthma
- cystic fibrosis

patterns of bronchiolitis are distinctive and are therefore classified by specific descriptive terminology, such as respiratory bronchiolitis, follicular bronchiolitis, diffuse panbronchiolitis and obliterative bronchiolitis.

C. Clinical features

The symptoms and signs of bronchiolitis are nonspecific and polymorphous. The course is usually chronic, but it may be acute or subacute. Pulmonary function tests most frequently demonstrate an obstructive pattern but they may also be characterized by a restrictive profile or they may even be normal in the early phases of disease[11]. Specific laboratory markers for bronchiolitis have not yet been identified.

D. Imaging features: high resolution computerized tomography (HRCT)

High resolution computerized tomography (HRCT) plays a major role in the diagnosis of bronchiolitis[12]. Certain patterns of abnormality on HRCT are highly suggestive of the diagnosis, and in many cases the findings on CT provide the first indication of the presence of small airways disease. HRCT also provides the most reliable assessment of both the extent and the severity of disease, and is a reliable, noninvasive method for assessing response to treatment without the need for repeated histological evaluation. Interpretation of the HRCT findings of bronchiolitis requires an understanding of the anatomy of the secondary pulmonary lobule. The final, purely conducting, bronchiole is the terminal bronchiole. Distal to terminal bronchioles is the gas-exchanging unit of the lung, known as acinus (primary pulmonary lobule), comprising respiratory bronchioles (that have both alveolated and nonalveolated walls), alveolar ducts and alveoli. The bronchioles and their accompanying pulmonary artery branches are located near the centre of the secondary pulmonary lobules, and the pulmonary veins are located in the interlobular septa[1]. Normal bronchioles cannot be identified on CT because their diameter is too small (1 mm or less) and their walls are too thin (0.1 mm or less). The smallest intralobular structures that are visible on HRCT are the intralobular pulmonary arteries measuring approximately 0.2 mm in diameter[13], which corresponds to the level of the tip of the terminal bronchiole and the first-generation respiratory bronchiole. It is normally possible to recognize the centrilobular portion as an area around the tip of the visible intrapulmonary pulmonary artery on HRCT. Although normal bronchioles cannot be visualized, the presence of bronchiolar disease may result in direct and indirect visible signs on HRCT[2,12]. Direct signs result from the presence of bronchiolar secretions, bronchiolar wall thickening, or peribronchiolar inflammation. Direct signs include centrilobular nodules, branching or Y-shaped centrilobular opacities ("tree-in-bud" opacities) and, occasionally, small centrilobular lucencies due to bronchiolectasis. Centrilobular opacities can be recognized because they are centred 3 mm or more from the periphery of the secondary lobule, that is, from the interlobular septa, pleura, and large pulmonary vessels. Indirect signs include areas of decreased attenuation and vascularity (mosaic attenuation and perfusion pattern) on inspiratory scans and areas of air trapping on HRCT scans obtained at end expiration[14]. Centrilobular nodules are observed in several forms of bronchiolitis, including infectious bronchiolitis, acute noninfectious bronchiolitis (e.g., aspiration bronchiolitis) respiratory bronchiolitis, follicular bronchiolitis and diffuse panbronchiolitis. They are also common in patients with cellular bronchiolitis associated with hypersensitivity pneumonitis. A tree-in-bud pattern is seen most commonly in infectious bronchiolitis. A mosaic attenuation and perfusion pattern and air trapping on expiratory CT are characteristic of obliterative (constrictive) bronchiolitis[14].

PRIMARY BRONCHIOLAR DISORDERS

1. Constrictive Bronchiolitis [Obliterative Bronchiolitis (OB), Bronchiolitis Obliterans]

Wilhelm Lange's original description of "bronchiolitis obliterans" in 1901 was of two patients with what would now be termed "cryptogenic organizing pneumonia." In 1973 Gosink and colleagues applied the term "bronchiolitis obliterans" to a heterogeneous group of patients some of whom had submucosal and peribronchiolar fibrosis resulting in extrinsic narrowing and obliteration of the bronchiolar lumen referred to as constrictive bronchiolitis. Most of the patients described by these authors most likely had cryptogenic organizing pneumonia. In the years since these reports, the term "bronchiolitis obliterans" has been used for a variety of unrelated clinicopathological conditions. Pathologically, constrictive bronchiolitis is characterized by a distinctive pattern of submucosal and peribronchiolar fibrosis resulting ultimately in complete cicatrization of the bronchiolar lumen. The fibrosing inflammatory process surrounds rather than fills the lumen, resulting in extrinsic compression and obliteration of the

airway[7]. Areas of fibrosis appear patchy and subtle, even in severely affected patients, and thus the diagnosis can be missed if the lesions are inadequately sampled, rendering surgical lung biopsy necessary[15] when histological confirmation is required. Constrictive bronchiolitis may result from a number of causes, such as connective tissue disorders[16] (most common), infections, inhalational injury, chronic hypersensitivity pneumonitis, drugs, organ transplantation, and many other conditions, or it may occasionally be idiopathic (cryptogenic) (Table 2). The evidence supporting some of these associations is relatively tenuous and the documentation consists of case reports or small case series. It is likely that the pathogenetic mechanisms of constrictive bronchiolitis vary according to the specific cause or underlying disease, although it is apparent that various forms of insult can eventually give rise to a similar histopathological lesion. Rheumatoid arthritis–associated constrictive bronchiolitis occurs principally in women in their fifth to sixth decades of life, most of whom have long-standing rheumatoid arthritis[15,17], although in rare cases pulmonary abnormalities antedate the rheumatoid manifestations. Although earlier reports of constrictive bronchiolitis in rheumatoid arthritis described a rapidly progressive course that was often fatal, it has recently become clear that there is considerable heterogeneity in the rapidity of progression, with a number of patients deteriorating slowly. Minor and subclinical degrees of constrictive bronchiolitis are probably present in many patients with rheumatoid arthritis. Penicillamine therapy has been implicated as a potential aetiological factor in some of these patients.

TABLE 2. Conditions Associated with Constrictive Bronchiolitis

Postinfectious
Viruses (mainly adenovirus and respiratory syncytial virus, influenza, parainfluenza), Mycoplasma, Pneumocystis
Connective tissue diseases
Rheumatoid arthritis, Sjögren's syndrome, eosinophilic fasciitis; occasionally systemic lupus erythematosus, scleroderma, polymyositis and dermatomyositis
Inhalational injury
NO_2 (silo filler's lung), SO_2, ammonia, chlorine, phosgene, smoke inhalation, fly ash, volatile butter-flavouring ingredients (microwave popcorn production workers)
Allograft recipients
Lung, heart-lung, and stem cell transplantation
Drugs
Penicillamine, gold, cocaine, lomustine, etc.
Ingested toxins
Sauropus androgynus (shrub used for weight reduction in Southeast Asia)
Miscellaneous
Chronic hypersensitivity pneumonitis, multiple carcinoid tumourlets, ulcerative colitis, gastrooesophageal reflux, primary biliary cirrhosis, Stevens-Johnson syndrome, chronic asthma, neuroendocrine cell hyperplasia, paraneoplastic pemphigus
Cryptogenic (idiopathic)
Rare, usually older women

Constrictive bronchiolitis with airflow obstruction has been known to complicate a variety of pulmonary infections and inhalational injury. Viral infections, particularly those due to childhood respiratory syncytial virus and adenovirus, have been most frequently implicated. One of the long-term complications of postinfectious constrictive bronchiolitis occurring in childhood is the development of the Swyer–James (or MacLeod's) syndrome. Constrictive bronchiolitis after noxious inhalational injury, e.g., ammonia, presents as cough and progressive dyspnoea beginning days to weeks after recovery from the acute exposure. Patients with allogeneic or autologous bone marrow transplantation, heart-lung transplantation, or lung transplantation may develop constrictive bronchiolitis as a chronic rejection phenomenon. This problem is a major threat to long-term survival in these transplant recipients and may affect up to 65% of patients at 5 years after lung transplantation[18-20]. Constrictive bronchiolitis is the primary cause of late death after lung transplantation. The clinical features of the syndrome include productive cough, dyspnoea on exertion with progressive deterioration, and irreversible airflow obstruction, with only moderate reduction of the diffusing capacity. Arterial hypoxaemia and hypocapnia are nearly always present. Confirming the diagnosis of constrictive bronchiolitis in transplant recipients by transbronchial lung biopsy is problematic because of the patchy distribution of the lesions and difficulty in obtaining adequate samples of bronchioles. Thus, the phenomenon of progressive airway obstruction in transplant recipients is termed "bronchiolitis obliterans syndrome" (BOS), which is a clinical diagnosis, defined physiologically by a decrement in FEV_1 of 20% or more below a stable baseline.

The Pathophysiology of Bronchiolitis Obliterans Syndrome (BOS)[21,22]

OB/BOS probably results from a primary insult (is-

chaemia-reperfusion injury, acute rejection, infection, aspiration, etc.) to the airway epithelium, which may be either unique and severe or repetitive and less severe, and either immunological (HLA-antibody driven) or nonimmunological (innate and adaptive immune response). This insult upregulates dendritic cells in the epithelium, attracting more inflammatory cells (at first, lymphocytes) leading to epithelial damage and inflammation, with resultant production of chemokines and cytokines (IL-1, -2, -4, -6, -8, -10, -12, -13, etc.) from the epithelium itself, smooth muscle cells, macrophages, and neutrophils. Activated neutrophils may further aggravate epithelial damage via the production of reactive oxygen species and metalloproteinases. After an initial inflammatory phase, a fibroproliferative phase occurs, driven by myriad growth factors, including platelet-derived growth factor (PDGF), insulin growth factor (IGF), fibroblast growth factor (FGF), transforming growth factor-b (TGF-b), endothelin-1 (ET-1), etc., leading to proliferation of smooth muscle cells and fibroblasts (myofibroblasts) and eventually resulting in the deposition of collagen and the typical fibrous, obliterative lesions of the airways. Although it was initially thought that OB/BOS is characterized by a predominantly neutrophilic airways inflammation with upregulation of airway IL-8, it is becoming clear that at least two different BOS phenotypes can be distinguished, based on the results achieved with azithromycin as additive treatment for patients with BOS. Chronic allograft dysfunction may present as a neutrophilic airways inflammation, starting rather early after lung transplantation and characterized by an increase in FEV1 under treatment with azithromycin[23], whereas the other phenotype shows an absence of neutrophilic airway inflammation, starts rather late after transplantation and does not respond to azithromycin. As a consequence, the first phenotype can no longer be considered as BOS, since BOS is defined as a largely irreversible airways obstruction. It has therefore been proposed that this phenotype should be renamed as neutrophilic reversible allograft dysfunction (NRAD), while the second phenotype truly represents OB/BOS, or fibrotic BOS (fBOS) (Table 3).

Other causes

Other causes and associates of constrictive bronchiolitis that have been identified include neuroendocrine cell hyperplasia[24] or multiple carcinoid tumourlets[25], paraneoplastic pemphigus[26], inflammatory bowel disease[27], ingestion of uncooked *Sauropus androgynus*[28] (a vegetable with reported weight control properties), gold therapy, and penicillamine therapy[29]. There are probably multiple mechanisms through which the lesion of constrictive bronchiolitis develops. For example, constrictive bronchiolitis occurring in patients with paraneoplastic pemphigus involves deposition of IgG autoantibodies on the surface of bronchial epithelial cells and lysis of the acanthoid layer[30]. When constrictive bronchiolitis occurs with no identifiable cause, it is referred to as cryptogenic constrictive bronchiolitis[31]. This is rare and occurs mostly in women. Patients with constrictive bronchiolitis present with a persistent cough and worsening dyspnoea. Basilar inspiratory crackles may be heard on auscultation of the lungs in some patients. The functional manifestations of constrictive bronchiolitis[32] are those of airflow obstruction and air trapping, as demonstrated by a reduction in FEV_1 and an increase in RV and the ratio of RV to total lung capacity (TLC). The TLC is often normal until the late stages of the disease. The diffusing capacity is commonly reduced, and there is no significant response to bronchodilators[33]. Chest radiography in patients with constrictive bronchiolitis demonstrates normal findings or nonspecific abnormalities, including peripheral attenuation of the vascular markings and vari-

TABLE 3. Characteristics of the Two Phenotypes of Bronchiolitis Obliterans Syndrome (BOS)

	Neutrophilic Reversible Allograft Dysfunction (NRAD)	**Fibroproliferative BOS (fBOS)**
BAL	Excess neutrophils (>15%)	Neutrophils <15%
Clinical features	Coarse crackles, increased sputum production	No crackles, no sputum
Time of onset	Early after transplantation (<1 yr)	Later (>1 yr)
Progression	Slow (several years)	Rapid (<6–12 months)
Histology	Inflammatory, ends up in fibrosis	Pure fibrosis (?)
Radiology	Airway wall thickening, mucus plugging, bronchiectasis	Air trapping, consolidation
Effect of azithromycin	Improvement of FEV1 (reversible)	No effect on FEV1 (irreversible)

able degrees of hyperinflation, resulting in flattening of the diaphragm and increase in the retrosternal airspace. If serial radiographs are available, the progressive increase in lung volume may be appreciated. Ancillary findings occasionally include prominent bronchial markings, bronchiectasis, and nodular or reticulonodular opacities. HRCT demonstrates sharply defined mosaic (multilobular) areas of decreased attenuation and vascularity, blood flow redistribution to normal areas, evidence of air-trapping (accentuated on expiratory views), peripheral cylindric bronchiectasis, and bronchial wall thickening[15]. Air trapping can be considered abnormal when affecting more than 25% of the total volume of the lung and not limited to the superior segment of the lower lobe or the lingula tip. Although these HRCT findings are not specific for constrictive bronchiolitis, this constellation of features can be considered diagnostic in the appropriate clinical setting[12]. The radiological finding of a mosaic pattern of lung attenuation can be due to pulmonary vascular disease and diffuse parenchymal disease as well as small airway disease. Expiratory HRCT imaging and contrast enhancement of vasculature can distinguish between these differential diagnostic possibilities[13]. Additional features may be detected on HRCT in constrictive bronchiolitis, depending on the underlying cause.

2. Acute infectious bronchiolitis

Infection is the most common cause of acute bronchiolitis, although infectious causes are more frequent in children than adults[34]. The usual infective agents incriminated in young children include viruses and *Mycoplasma pneumoniae,* organisms that have a propensity to infect and injure the epithelial cells of the respiratory tract; however, in older children and adults other bacterial agents (e.g., *Legionella, Chlamydia*)[35,36] and fungi (particularly *Aspergillus* in immunocompromised patients) have been identified. Bronchiolitis is usually self-limiting, and complete recovery usually occurs within days to weeks[37]. Bronchiolitis in infancy has been associated with an increased risk of subsequent wheezing, bronchial hyperactivity and early childhood asthma[38] but a direct link to chronic obstructive pulmonary disease has not been shown. Histopathological studies of acute infectious bronchiolitis have shown intense acute and chronic inflammation of the small bronchioles, with the presence of inflammatory cells, mainly of neutrophils, in the walls of the bronchioles. There may be associated oedema, as well as inflammatory exudate and mucus in the bronchiolar lumen[39,40]. These histological findings account for the centrilobular nodules and branching opacities (tree-in-bud pattern) seen on HRCT. Necrosis of the bronchiolar epithelium with sloughing may occur in severe cases[41]. Biopsy is seldom required for the diagnosis of infectious bronchiolitis. Acute bronchiolitis is the most common disease of the lower respiratory tract during the first year of life and occurs in annual epidemics during the winter months. In children, the usual presentation is an acute viral-like illness with mild coryza and sneezing followed several days later by cough, dyspnoea, tachypnoea, tachycardia, fever, nasal flaring, chest wall retraction, expiratory wheezing, and, in severe cases, cyanosis. Respiratory failure is unusual. The clinical presentation of infectious bronchiolitis in adults is ill defined; no systematic study of its characteristics has been reported. Most patients have a history of an upper respiratory tract illness that precedes the onset of dyspnoea with exertion, cough, tachypnoea, fever, and wheezing[42]. Because the small airways in adults contribute less to total pulmonary resistance, acute infectious bronchiolitis may spare adults the severe symptoms characteristic of bronchiolitis in infants. Measles, varicella zoster, and pertussis have been reported to cause OB in adults. A number of adults have developed an acute or subacute diffuse ventilatory obstruction that has occasionally been fatal. Pulmonary function testing demonstrates the findings of airway obstruction. The radiological pattern of acute bronchiolitis is variable. Chest radiography typically demonstrates hyperinflation (due to partial small airway obstruction). Tiny nodules, linear opacities, patchy ground-glass opacities and collapse (atelectasis) may sometimes be seen. The radiographic findings of acute bronchiolitis in infants and children consist of bronchial wall thickening and peribronchial (central) areas of consolidation, whereas in adults[43] a bilateral nodular or reticulonodular pattern may be seen. Progression to bronchopneumonia results in patchy bilateral areas of consolidation (Figure 2). The characteristic HRCT findings of infectious bronchiolitis in adults consist of centrilobular nodules and branching opacities (tree-in-bud pattern), which is highly suggestive of infection of the small airways[44]. It is seen most commonly in infectious bronchiolitis, bronchopneumonia, and endobronchial spreading of mycobacterial infection. The centrilobular nodules and tree-in-bud pattern in infectious bronchiolitis tend to be well defined and usually have a patchy unilateral or bilateral asymmetrical distribution (Figure 3). The nodules usually measure 2-5 mm in diameter. Progression to bronchopneumonia is delineated radiographically by 5- to 10-mm diameter

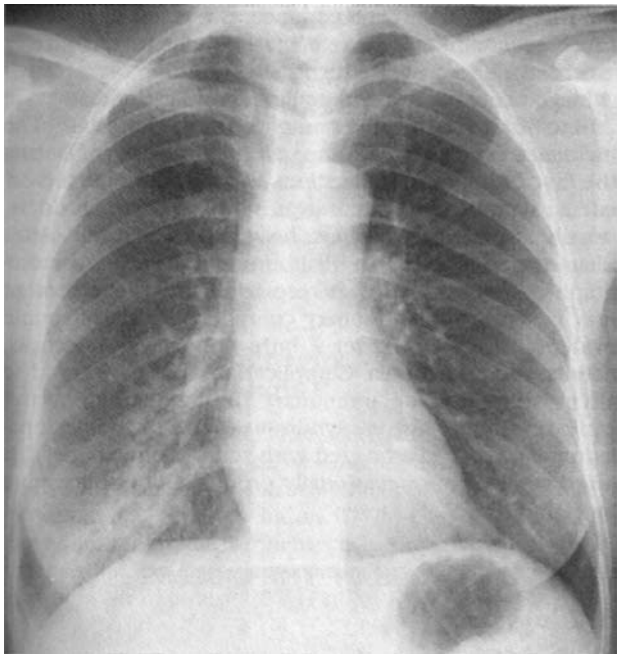


FIGURE 2. Posteroanterior chest radiograph of a 48 year-old patient with Mycoplasma bronchiolitis and bronchopneumonia showing poorly defined nodular opacities and foci of consolidation in the right lower lobe.

airspace nodules and patchy lobular, subsegmental, or segmental areas of ground-glass opacity or consolidation. Overall, the mortality rate of acute bronchiolitis is less than 1%. In a small subset of patients, healing of acute bronchiolitis can lead to fibrous obliteration of small airways resulting in chronic airflow limitation, i.e., constrictive bronchiolitis. This phenomenon is seen most often after adenovirus infection, but also after measles, pertussis, mycoplasma, influenza A, and other infections. In some of these cases, unilateral hyperlucent lung and/or a combination of geographic hyperlucency, central bronchiectasis, and vascular attenuation may be seen (Swyer–James syndrome)[45] (Figure 4). Originally this disorder was thought to be restricted to one lung and one lobe, but the advent of CT has made it increasingly clear that bilateral involvement is the rule rather than an exception[46] (Figure 5).

3. Diffuse panbronchiolitis

Diffuse panbronchiolitis is a distinctive chronic inflammatory disease of the respiratory bronchioles and surrounding alveoli, with involvement of the paranasal sinuses. Histologically, all layers of the walls of the respiratory bronchioles are involved (hence, pan-bronchiolitis). It

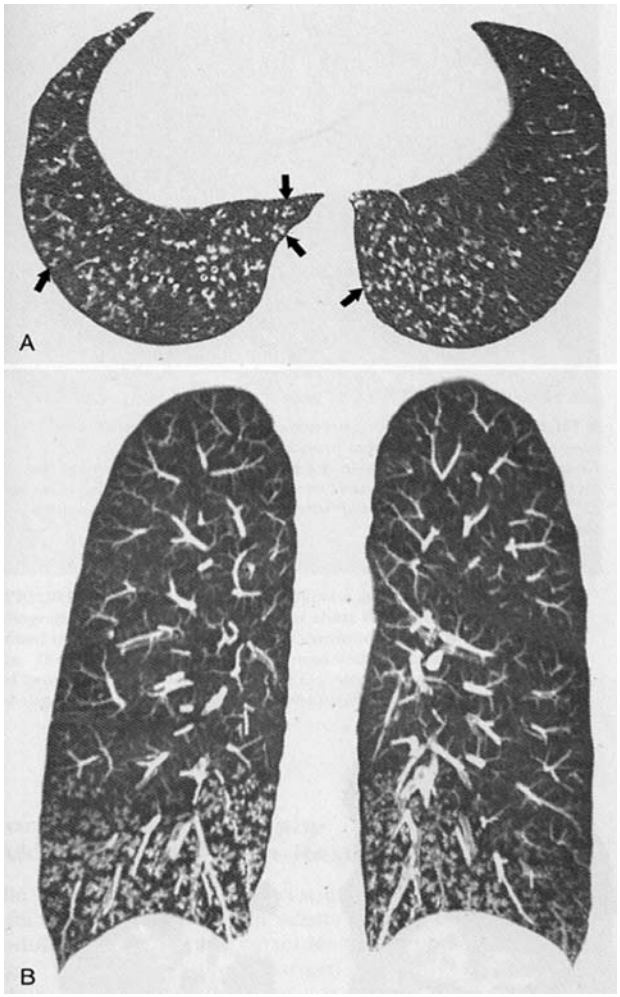


FIGURE 3. Tree-in-bud pattern in infectious bronchiolitis. A. High-resolution CT. B. Coronal maximum-intensity projection image.

is a disease of unknown aetiology and pathogenesis and is mainly restricted to Japan but has also been reported in China and Korea, and a few case reports of the disease in whites in the United States have appeared[47]. A familial predisposition with a significant increase in HLA-Bw54[48] (63%) has been described. The genetic and ethnic background observed in connection with this unique syndrome may be explained on the basis of HLA-Bw54 or its related haplotype being confined primarily to certain Asian races. HLA-Bw54 is associated with a 13.3-fold increase in risk for diffuse panbronchiolitis. HLA-Bw54 may also be a useful marker in the differential diagnosis of diffuse panbronchiolitis, since the frequency of this haplotype in the general population is very low (11.8%). Environmental factors also appear important, since the disorder is very

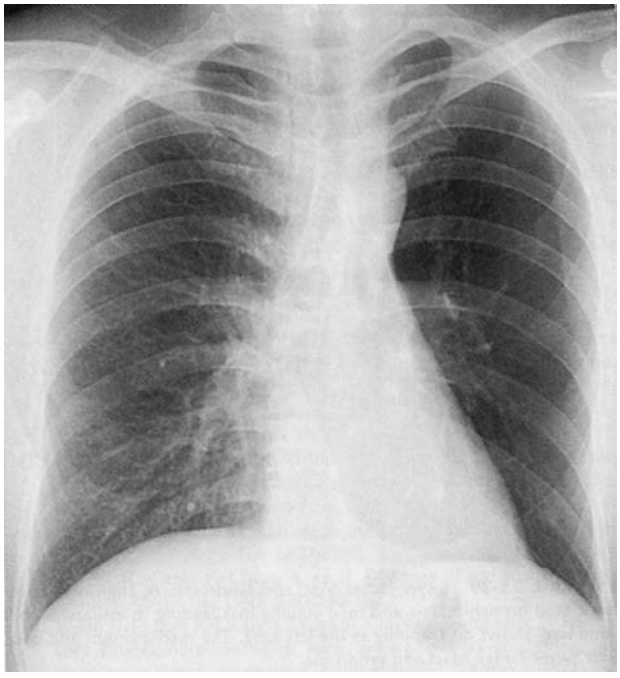


FIGURE 4. Chest radiograph of a 40 year-old asymptomatic man with Swyer-James-MacLeod syndrome, showing hyperlucency and decreased vascularity of the left lung, with the mediastinum shifted to the left, consistent with hypoplastic left lung with decreased volume.

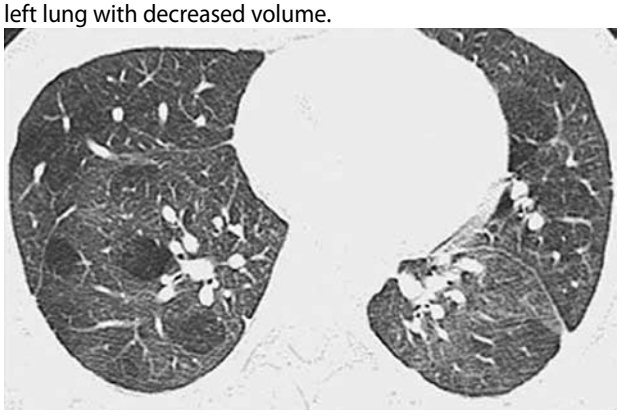


FIGURE 5. High-resolution CT image of the chest demonstrating asymmetric patchy lobular air trapping with bilateral diminished vascularity in the lungs from Swyer-James-Macleod syndrome.

uncommon in persons of Asian ancestry living abroad. Diffuse panbronchiolitis is more prevalent in men, with a 2:1 male-to-female ratio. The peak incidence occurs between the fourth and seventh decades of life; the mean age at presentation is 50 years. Neither cigarette smoking nor occupational exposures have been shown to be predisposing factors. The usual presenting symptoms are chronic cough, expectoration of copious amounts of purulent sputum and exertional dyspnoea. The majority of patients (75%-100%) also complain of chronic sinusitis, suggesting that there may be an underlying abnormality of ciliary function. The sinus problems often precede chest symptoms by years or decades. Chest auscultation may reveal decreased breath sounds with coarse crackles or wheezing. Digital clubbing is not a feature. The histopathological findings in diffuse panbronchiolitis are characteristic and consist of bronchiolocentric infiltration with lymphocytes, plasma cells, and foamy histiocytes in the walls of the respiratory bronchioles, the alveolar ducts, and, to a lesser extent, the adjacent alveoli[49]. Intraluminal aggregates of neutrophils and mucus can be prominent. The organization of intraluminal exudates may result in polypoid plugs. In addition, marked increase in the number of dendritic cells has been found in both the bronchiolar epithelium and the submucosal tissues of patients with diffuse panbronchiolitis. Bronchoalveolar lavage (BAL) fluid analysis reveals marked neutrophilia, a decreased CD4/CD8 ratio, an increase in absolute number of the CD8+HLA-DR+ cells and CD3+gammadelta+ cells. IL-8, leukotriene B4[50] and defensins have been reported to be present in elevated concentrations in the BAL fluid. Advanced disease is manifested by secondary ectasia of the proximal small bronchi. Although this pattern of bronchiolitis is characteristic of diffuse panbronchiolitis, almost identical changes have been described in a broad range of airway-centred disease processes, including bronchiectasis and rheumatoid arthritis–related bronchiolitis. The most characteristic laboratory feature associated with diffuse panbronchiolitis is the persistent, marked elevation of cold haemagglutinin titers, but mycoplasmal antibody titers are negative. Elevated leukocyte count and erythrocyte sedimentation rate (ESR) are common. Rheumatoid factor and serum Ca 19-9 may be elevated. Immunoglobulin levels are usually normal. In the early stages of the disease, the sputum generally contains normal flora, but infection and/or colonization of the airways with *H. influenza*, and occasionally with *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, or *Staphylococcus aureus* follows. Colonization with *Pseudomonas aeruginosa* eventually occurs, which appears to accelerate the destructive process. Pulmonary function testing generally demonstrates marked obstructive impairment, with at least three of the four abnormalities: FEV_1/FVC less than 70%, FVC less than 80% of the predicted value, RV greater than 150% of the predicted value, along with disorders of arterial blood gases with PO_2 less than 80 mmHg, with or

without hypercapnia. In some patients, a superimposed mild to moderate restriction may also be seen. The diffusing capacity is variably reduced. In general, patients with diffuse panbronchiolitis exhibit less bronchodilator responsiveness than do patients with chronic obstructive pulmonary disease (COPD). On chest radiography, diffuse panbronchiolitis is characterized by diffusely disseminated small (up to 5 mm in diameter), ill-defined nodular opacities, most prominent over the lung bases, and symmetrically distributed. Alternatively, a reticulonodular pattern may be evident. Mild to moderate hyperinflation may be seen. In the later stages, the radiographic features of cylindric and cystic bronchiectasis may become evident. The findings on HRCT are quite characteristic but not specifically pathognomonic. They include small centrilobular nodules and branching linear opacities (tree-in-bud pattern), bronchiolectasis, bronchiectasis, bronchial wall thickening, and areas of decreased parenchymal attenuation and vascularity[51]. Peripheral air trapping is usually confirmed in expiratory films. The presence of these findings is related to the stage of the disease; the earliest manifestation consists of centrilobular nodular opacities, followed by distal branching opacities (secretion-filled bronchioles) that connect to the nodules, followed by cystic dilatation of the nodules (bronchiolectasis) and, eventually, bronchiectasis. Cystic bronchiectasis may be seen in the late stage. The natural history of diffuse panbronchiolitis is characterized by progressive respiratory dysfunction with episodic bacterial superinfection, often with *P. aeruginosa*. Colonization with *P. aeruginosa* appears to be associated with a worse prognosis. In one study, the 10-year survival rate for those infected with the organism was only 12% as compared with 73% for those who remained uninfected[52]. In advanced disease, patients succumb to chronic respiratory failure and cor pulmonale leading to death.

4. Respiratory bronchiolitis

Exposure to cigarette smoke results in various changes in the bronchioles, ranging from potentially reversible inflammatory reactions to fixed scarring. Respiratory bronchiolitis is a distinct pathological entity, first described by Niewoehner and colleagues, almost exclusively found in cigarette smokers. Rarely, respiratory bronchiolitis may occur in nonsmokers with other inhalational exposures, particularly asbestos dust. Respiratory bronchiolitis is identifiable histologically in virtually all smokers, but typically is not associated with symptoms of functional impairment. On occasion, respiratory bronchiolitis can be extensive, with diffuse parenchymal lung infiltrates, and may be accompanied by symptoms and functional evidence of lung disease, a syndrome referred to as respiratory bronchiolitis–associated interstitial lung disease (RB-ILD)[53]. Respiratory bronchiolitis is characterized histologically by intraluminal and peribronchiolar airspace accumulation of alveolar macrophages containing a fine brown cytoplasmic pigment (smoker's macrophages). This pigmentation most likely represents the metabolites of cigarette smoke. Other common findings include mild chronic inflammation and fibrosis of the bronchiolar walls, mild peribronchiolar mononuclear inflammatory infiltrate, and mild peribronchiolar fibrosis[54]. The intensity of macrophage pigmentation and of peribronchiolar fibrosis correlates with the number of pack-years smoked. By definition, respiratory bronchiolitis is not associated with symptoms, with the exception of a "smoker's cough". It is found incidentally in lung specimens of asymptomatic cigarette smokers. Respiratory bronchiolitis currently is thought to be a possible precursor to chronic lung disease in heavy smokers. Chest radiographs are usually normal, with no clear evidence of lung infiltrates or apparent airway abnormalities. Because the patients are almost always smokers, the radiograph may demonstrate findings of emphysema or bronchial wall thickening. Given the histological findings, poorly defined small nodular opacities or poorly defined areas of ground-glass opacity may be present in some patients. HRCT is usually normal or shows only centrilobular emphysema, but when abnormalities are present, the findings consist of poorly defined centrilobular micronodules (3-5 mm in diameter) with ground-glass rather than soft tissue attenuation or patchy bilateral ground-glass opacities[55]. These abnormalities can be diffuse, but most commonly involve predominantly or exclusively the upper lobes (Figure 6). The main differential diagnosis of respiratory bronchiolitis on HRCT is hypersensitivity pneumonitis, which also usually manifests with poorly defined centrilobular nodules and ground-glass opacities that can be diffuse, but tend to involve mainly the lower lung zones. Another common manifestation of hypersensitivity pneumonitis is the presence of focal air trapping, frequently restricted to secondary pulmonary nodules. Upper lobe predominance of centrilobular nodules and association with emphysema favour the diagnosis of respiratory bronchiolitis; diffuse parenchymal involvement, mainly in the lower lobes, with areas of lobular air trapping is more consistent with hypersensitivity pneumonitis. However, more important for the differential diagnosis is the history

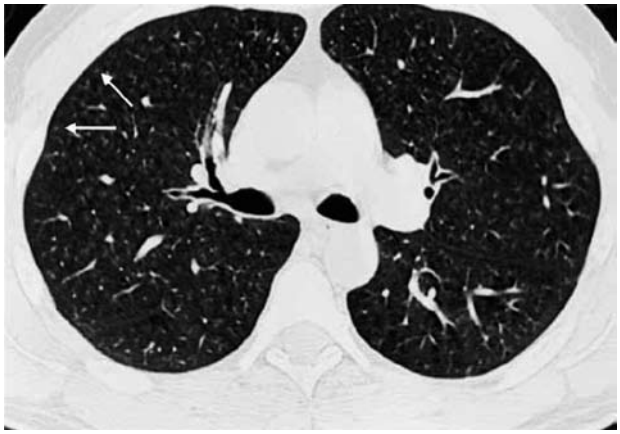


FIGURE 6. High-resolution CT image of the lung showing diffuse, poorly defined centrilobular nodules (arrows). In acute respiratory bronchiolitis the nodular opacities tend to be more poorly circumscribed than in chronic bronchiolitis, where the centrilobular nodular opacities and branched tubular opacities tend to be better circumscribed.

of either possible exposure to organic dust or of cigarette smoking. Cigarette smokers have a lower prevalence of hypersensitivity pneumonitis than nonsmokers. BAL yields increased cellularity in hypersensitivity pneumonitis, than in smokers. The increased cellularity is due to an increase in macrophages and (to a lesser degree) lymphocytes. The diagnosis is usually made on surgical biopsy, which demonstrates the characteristic pigmented "smoker's macrophages". There is an overlap between RB-ILD and desquamative interstitial pneumonitis (DIP). Some authors suggest that RB-ILD is a precursor of DIP or a less severe form of the same fundamental lesion[56].

5. Follicular bronchiolitis

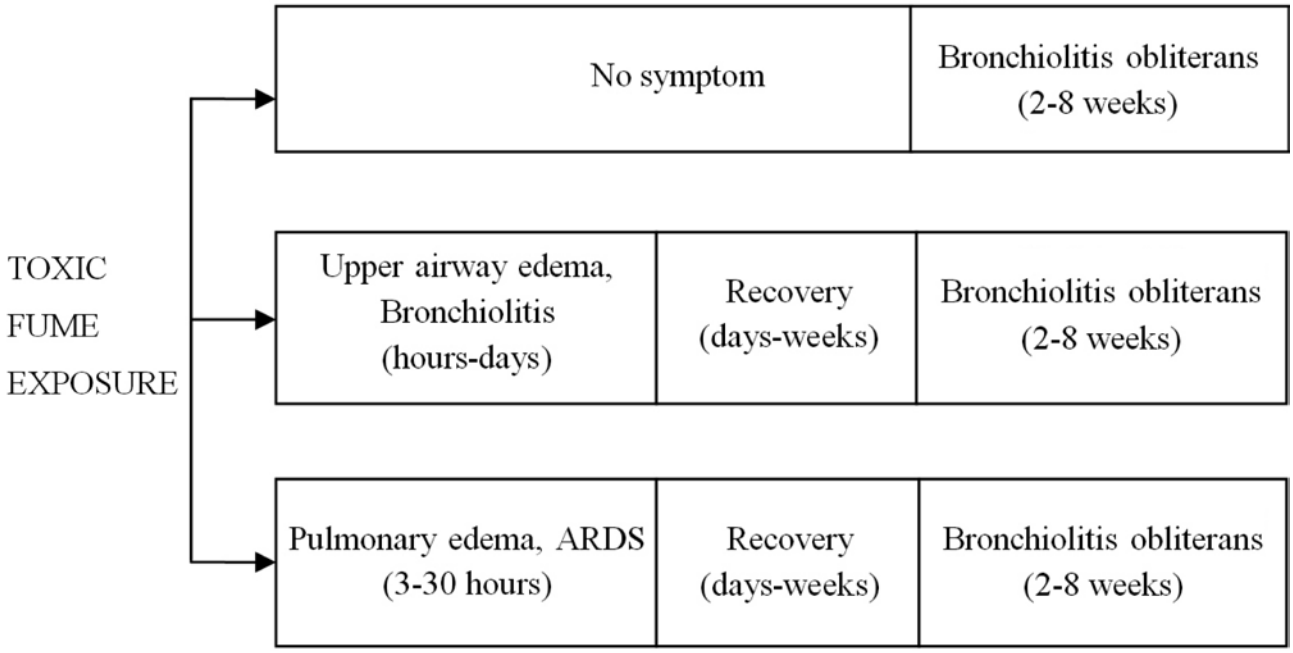
Follicular bronchiolitis is characterized histologically by the presence of hyperplastic lymphoid follicles with reactive germinal centres distributed along bronchovascular bundles (in the walls of bronchioles, and, to some extent, along bronchi, interlobular septa and pleura). It represents lymphoid hyperplasia in response to an extrinsic immune stimulus or altered systemic immune response. It has been described in primary pulmonary lymphoid hyperplasia or as a secondary event in patients with bronchiectasis affecting proximal large airways, and in association with connective tissue diseases[57] (particularly rheumatoid arthritis and Sjögren's syndrome), immunodeficiency syndromes including AIDS, pulmonary infections, or ill-defined hypersensitivity reactions[58]. Follicular bronchiolitis has been reported in patients with common acquired hypogammaglobulinaemia, in whom there is a higher incidence of lymphoproliferative disease. In patients with primary lymphoid hyperplasia, peribronchiolar lymphocytic infiltration into the interstitium often accompanies the peribronchiolar lymphoid aggregates and overlaps with lymphoid interstitial pneumonia. Most patients complain of slowly progressive exertional dyspnoea. Variable pulmonary functional impairment has been reported, including obstructive, restrictive, and mixed patterns. The predominant finding on chest radiography is bilateral, small nodular, or reticulonodular infiltrates with intrathoracic adenopathy, but the appearance may be normal. The cardinal features of follicular bronchiolitis on HRCT consist of centrilobular nodules measuring 3-12 mm in diameter, associated with peribronchial nodules and patchy areas of ground-glass opacity. Nodules and ground-glass opacities are generally bilateral and diffuse in distribution[59]. Mild bronchial dilatation with wall thickening is seen in some cases (Figure 7). Mosaic perfusion, pleural effusion and areas of honeycombing are not seen.

6. Bronchiolitis related to toxic gases or fumes

The inhalation of fumes (fine particulates), toxic gases, mists, or organic material constitutes a significant industrial and environmental hazard in many settings. Exposure can result in acute lung injury with subtle or severe clinical illness; bronchiolitis may be either the major manifestation or a minor component of such injury. Because they are highly soluble, irritants such as sulfur dioxide and ammonia dissolve in the lining fluid of the upper airways, where they cause the primary damage. Less soluble gases such as nitrous oxide (NO2) and phosgene pass into the peripheral airways, where they cause inflammatory changes in the bronchioles and alveoli (Figure 8).

After exposure to toxic fumes, three clinical patterns may develop[7].

The oxides of nitrogen are the most common and best-described gaseous agents known to cause acute and chronic lung injury. Silo filler's disease is a well-studied example. The estimated annual incidence of silo filler's disease[60,61] is 5 cases per 100,000 silo associated farm workers per year. Most cases occur during the harvest period (September and October). NO2 and nitrogen tetroxide are responsible for the injury. For 3-10 days after a silo has been filled, the fresh silage produces nitric oxide (NO), which on contact with air oxidizes to form NO2. NO2 is relatively insoluble, and after inhala-



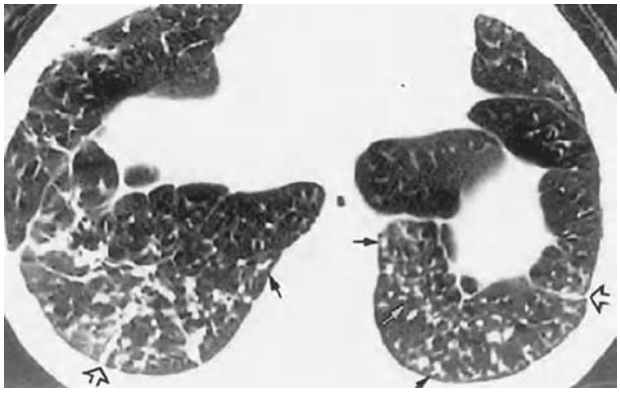


FIGURE 7. A 65 year-old patient suffering from follicular bronchiolitis secondary to rheumatoid arthritis. High-resolution CT image through the lower lung zones demonstrating multiple well-defined nodules in a centrilobular distribution, several of which are clustered (thin arrows). Mild interlobular septal thickening (thick arrows) is also depicted.

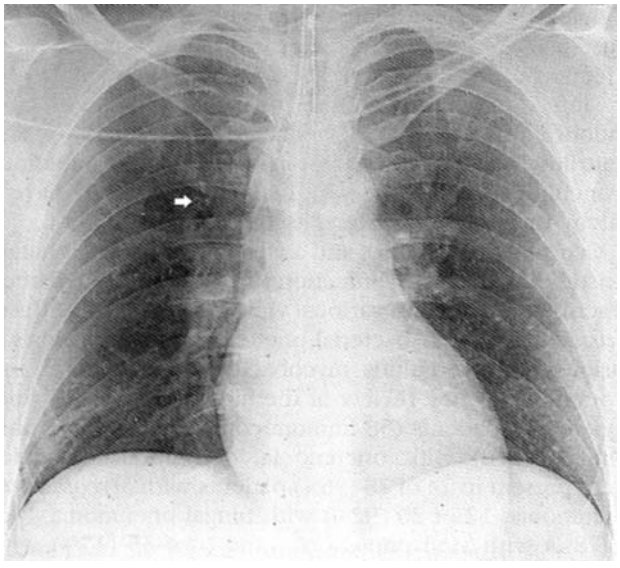


FIGURE 8. Acute smoke inhalation. Chest radiograph showing bronchial wall thickening (arrow), poorly defined small nodular opacitie,s mainly in the upper lobes, and prominence of the pulmonary vessels. The patient was a 35 year-old man with acute smoke inhalation from a home fire.

tion, the gas reaches the periphery of the lung, where it combines with water to form nitric and nitrous acids, which are powerful oxidants capable of causing severe tissue injury. Unlike highly water-soluble gases, such as ammonia, chlorine, and sulfur dioxide, NO2 is less irritating to the mucous membranes of the nasal and upper airways. The gas produces a yellow-brown haze and has an acrid, ammonia-like odour. Clinical manifestations of exposure to NO2 depend on the concentration of the inhaled gas and the duration of exposure. Three clinical patterns or phases may follow exposure[41], although all the phases may not appear in an individual patient. Progression to death may be an outcome at any stage.

Acute Phase

Acutely, during milder exposure, people may develop upper airway and visual disturbances, cough, dyspnoea, fatigue, cyanosis, vomiting, haemoptysis, hypoxaemia, vertigo, somnolence, headache, emotional difficulties, and loss of consciousness. These findings usually resolve within hours, but they may persist for several weeks; complete recovery without obvious sequelae is usually observed. At higher concentrations of exposure, pulmonary oedema (so-called, "chemical pneumonitis") is a frequent complication in the early stages. Patients may be asymptomatic at the time of exposure, only to develop later (after 3 to 30 hours) the clinical picture of severe acute respiratory distress syndrome. During this acute phase, patients who develop pulmonary oedema and acute respiratory distress syndrome have significant pulmonary dysfunction. Hypoxaemia is secondary to ventilation-perfusion mismatching as a result of altered airway dynamics and interstitial and alveolar oedema, impaired diffusing capacity, and methaemoglobinaemia that occurs when nitrate ions react with haemoglobin. Severe metabolic acidosis occurs because of the NO2 dissolving in body fluids, resulting in formation of nitrous and nitric acids, and lactic acidosis resulting from tissue hypoxia. Systemic hypertension may be present. Recovery without long-term sequelae is usual, but death may occur at this stage. The radiographic manifestations during this stage include pulmonary oedema (i.e., alveolar filling). In survivors, these changes subside rapidly. Physiological studies reveal the simultaneous occurrence of restrictive and obstructive ventilatory defects; the former is manifest as a shift in the static pressure-volume curve downward and to the right. These abnormalities gradually resolve in survivors. Histopathological findings, as determined from autopsy studies, include marked intra-alveolar oedema and exudation, and thickening of the alveolar walls with lymphocytic cellular infiltrates.

Subacute Phase

In patients who progress to the second phase, physiological disturbances include hypoxaemia at rest or with exercise, and associated restrictive or obstructive pulmonary function abnormalities. The radiographic pattern in this late stage may be variable. A normal appearance may be seen on the chest film, but a miliary, or discretely nodular, pattern is thought to be characteristic of OB. Occasionally, only pulmonary hyperinflation is seen, usually accompanied by a progressive and irreversible obstructive ventilatory defect detected on lung function testing.

Chronic Phase

After recovery from the acute illness, or even in patients with no initial symptoms following exposure, recurrence or new onset of clinical illness may be seen 2 to 6 weeks later. This phase is characterized by the progressive onset of cough and dyspnoea. These patients may be identified in an early, asymptomatic stage from the appearance of mild hypoxaemia. Tachypnoea is present, with crackles on lung auscultation. Widespread proliferative bronchiolitis with marked intraluminal fibrous tissue proliferation arising in the bronchiolar wall (without organizing pneumonia) is found, especially in those with preceding pulmonary oedema, although these findings may occur as the initial manifestation of earlier exposure.

In general, although less than one third of people exposed die in the acute phase, the prognosis for survivors of toxic gas or fume inhalation is good. Some authors have suggested that lasting pulmonary disability is uncommon in silo filler's disease; others have identified a wide variety of functional derangements[62]. What functional abnormalities result from chronic, low-level exposure to NO2 is not clear. Education is the key in preventing this disease, since simple measures to reduce the NO2 levels in the specific situation, and use of approved respiratory protection equipment will eliminate the risk of injury.

7. Mineral Dust Airway Disease (MDAD)

Mineral dust exposure is classically associated with restrictive lung disease due to parenchymal fibrosis (pneumoconiosis). However, mineral dusts can also produce abnormalities in the small airways and airflow obstruction[63]. Mineral dust airway disease (MDAD) refers to deposition of inhaled dust around the small airways, with some associated fibrosis. This condition primarily affects respiratory bronchioles and sometimes alveolar ducts, causing increased fibrous tissue in the walls of the bronchioles with luminal narrowing, and is often accompanied by pigment deposition[64]. There is usually a chronic inflammatory response. The morphological features are distinguishable from respiratory bronchiolitis induced by tobacco smoke. This form of bronchiolar disease may occur with inhalation of a number of inorganic dusts, including asbestos, iron oxide, aluminum oxide, talc, mica, silica, silicate, and coal[65]. Abnormalities are observed in nonsmokers, but occur most commonly in heavily exposed workers who are also cigarette smokers, so that a synergistic role for

cigarette smoking appears likely[66,67]. The degree of fibrosis in the bronchiolar wall appears to be closely linked to local dust burden. This type of bronchiolar lesion appears to be a specific marker for mineral dust exposure. Little information is available regarding the pathogenesis of mineral dust airway disease. It has been suggested that the two factors involved are local dust accumulation and the inflammatory response to the dust. Among subjects exposed to mineral dusts, susceptibility to this bronchiolar lesion may be determined by the individual ability to clear these particles from the airways[63]. The inflammatory response induced by the dust probably leads to local production of fibrogenic factors involved in the morphogenesis of this lesion. Mineral dust bronchiolitis may be associated with an obstructive defect, although cigarette smoking with resultant emphysema have confounded the interpretation of some studies in this regard. Chest radiography and HRCT may demonstrate tiny ill-defined punctate opacities but little else is known regarding the clinical and radiological correlates of this bronchiolar disorder.

THERAPEUTIC APPROACH

In most clinical settings, constrictive bronchiolitis tends to be progressive and poorly responsive to treatment with bronchodilators. Corticosteroids may be of benefit, mainly during the early stage of the disease before the development of irreversible structural changes[6], as the progressive airflow limitation may result in respiratory failure and death. In cases of constrictive bronchiolitis secondary to rheumatoid arthritis, combination therapy with intravenous cyclophosphamide has been proposed[68]; the administration of etanercept (tumour necrosis factor [TNF]-*α* inhibitor)[69] and methotrexate has also been evaluated. Management of posttransplant BOS involves prevention of acute graft rejection in order to avert the occurrence of the syndrome, in combination with pharmacological intervention once it is diagnosed. There is evidence to suggest that augmentation of immunosuppression with early initiation of tacrolimus[70,71] and mycophenolate mofetil[72] or IL-2 receptor blockers[73] might reduce the incidence of acute rejection; however, this does not appear to prolong life after transplantation. Other strategies that have been proposed for the management of acute rejection are total lymphoid irradiation, extracorporeal photochemotherapy, ganciclovir prophylaxis and methotrexate, with variable results[74]. Use of statin medications has been associated with a reduced incidence of BOS syndrome after lung transplantation[75]. In recent years, it has been shown that the newer macrolides (azithromycin) may have a beneficial effect in patients with BOS after lung transplantation[76], with 35% of patients responding to azithromycin treatment with a mean increase in FEV1 of approximately 14%[22]. When all the medical treatments discussed above have no beneficial effect, and the FEV1 further deteriorates, patients should qualify for retransplantation. In a recent series, retransplantation for BOS has shown encouraging results, with a 62% survival after 5 yrs, mostly in patients undergoing retransplantation over 2 years after the first transplant[77].

Symptomatic treatment of acute infectious bronchiolitis with supplemental oxygen and adequate hydration is usually necessary. Bronchodilators, antibiotics, antiviral agents, and corticosteroids are frequently used in management, although no role has been proven for them and few controlled clinical trials on their efficacy have been performed[78,79,80]. For treatment of bronchiolitis in infancy, early combined therapy with dexamethasone and epinephrine has recently shown promising results compared with either drug used alone[81]. Elevated levels of cysteinyl leukotrienes have been reported in viral infections, and in one study the LRA montelukast was shown to reduce respiratory symptoms after respiratory syncytial virus bronchiolitis[82]. Corticosteroids are often used empirically in progressive disease in an attempt to reduce the severity of OB. Mechanical ventilation is rarely required, but it may be necessary if progressive respiratory failure ensues[83,84].

The optimal treatment for diffuse panbronchiolitis is unclear. Low-dose erythromycin (400-600 mg a day) is the preferred therapy and has shown some efficacy[85]. The beneficial effect of macrolides has been well established and is related to their ability to impair the production of proinflammatory cytokines, including IL-1í and IL-8, rather than to their bactericidal effect[86]. Erythromycin impairs neutrophil chemotaxis, neutrophil superoxide production, and neutrophil-derived elastolytic activity, and it decreases the number of neutrophils in BAL fluid following challenge with gram-negative bacteria[87]. In addition, erythromycin may produce a reduction in mucus production[11,88]. Finally, erythromycin has been shown to reduce the circulating pool of T lymphocytes bearing HLA-DR, a marker of cellular activation. After at least 3 months of therapy, a reduction in the extent of small nodular opacities, the severity of 'periairways' thickening, and the extent of mucus plugging can be seen on HRCT scanning, with a corresponding significant improvement

in lung function[11]. Corticosteroids are commonly used in treatment regimens, although there is a lack of evidence supporting their efficacy. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a role in controlling the bronchorrhoea associated with this disease by altering airway epithelial ion and water transport[89], although no controlled trials with NSAIDs have been performed. The routine use of β2-agonists or ipratropium bromide should be encouraged to promote mucociliary clearance and bronchodilation in patients with a component of reversible airway disease, and as a part of routine pulmonary toilet. In addition, treatment of coexisting sinus disease may help in the control of airway disease. Lung transplantation has been used in some patients, but there are reports of disease recurrence in the allograft of one patient[90]. The prognostic implications of follicular bronchiolitis are unclear. Treatment is generally directed to the underlying disease when such association is recognized. Patients with no identifiable underlying cause have generally been treated with bronchodilators and corticosteroids[91]. More recently, erythromycin therapy has been reported to be of benefit[92]. Smoking plays a major role in the pathogenesis of respiratory bronchiolitis, and smoking cessation has been associated with resolution of the symptoms and improvement in the radiological and pathophysiological abnormalities[93]. Corticosteroids may be required in refractory or recurrent cases, but smoking cessation should definitely be encouraged.

The treatment of patients exposed to NO2 or other toxic gases or fumes should include observation in the hospital for 48 hours, followed by evaluation at weekly or biweekly intervals for 6 to 8 weeks. When dysfunction occurs, treatment with corticosteroids should be started immediately[60]. Corticosteroid therapy has been demonstrated to be useful in the management of both the acute phase (pulmonary oedema) and the late phase (OB)[42]. Corticosteroids should be continued for a minimum of 8 weeks, since relapses have been reported with the earlier cessation of therapy[94]. Bronchodilators are occasionally helpful, but antibiotics should be used only when clinically indicated, when they should be directed at a specific pathogen. If methaemoglobinaemia is present, methylene blue should be administered at a dose of 2 mg/kg intravenously, followed by doses titrated according to the concentration of methaemoglobin in the blood[95]. For patients in whom this diagnosis is suspected, and for whom open lung biopsy or general anaesthesia is planned, some have suggested that nitrous oxide not be used as an anesthetic because of concern that it might lead to disease progression.

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