



The emerging spectrum of exposure-related bronchiolitis

Silpa D. Krefft^{a,b,c}, Carlyne D. Cool^{d,e}, and Cecile S. Rose^{a,b,c}

Purpose of review

Exposure-related bronchiolitis is increasingly recognized as an important but challenging clinical diagnosis. Acute and chronic inhalational exposures are associated with variable clinical presentations and a spectrum of histopathologic abnormalities affecting the small airways. This review provides an overview of the histologic patterns and occupational settings for exposure-related bronchiolitis, along with recent advances in disease diagnosis and management.

Recent findings

The entire histopathologic spectrum of bronchiolitis (constrictive, obliterative, proliferative, lymphocytic, respiratory) has been reported in exposure-related bronchiolitis. Recent studies have shown that lung clearance index testing and impulse oscillometry are more sensitive than spirometry in detecting small airways abnormalities and may augment the diagnosis of occupational bronchiolitis. Prognosis in indolent occupational bronchiolitis appears more favorable than some other types of bronchiolitis but is variable depending on the extent of bronchiolar inflammation and the stage of disease at which exposure removal occurs.

Summary

No specific histopathologic pattern of bronchiolitis is pathognomonic for occupational bronchiolitis as one or more histologic patterns may be present. A high index of suspicion is needed for exposure and disease recognition. Recent advances that may aid in diagnosis include transbronchial cryobiopsy, lung clearance index testing, and impulse oscillometry, although further research is needed.

Keywords

constrictive, obliterative, occupational, respiratory bronchiolitis

INTRODUCTION

The diagnosis of bronchiolitis has received increasing attention in the occupational/environmental medical community as new causes and exposures have been identified and with the availability of newer diagnostic tools that may improve disease recognition. Classification of bronchiolar disorders is commonly based on either the clinical setting in which they occur or on lung histopathologic findings. There are seven major clinical categories of bronchiolitis: occupational or environmental exposure-related bronchiolitis, panbronchiolitis, autoimmune or inflammatory bowel disease bronchiolitis, bronchiolitis obliterans syndrome following lung or stem cell transplantation, drug-induced bronchiolitis, and infectious or postinfectious bronchiolitis [1–9]. Bronchiolitis also has been described in association with rare entities such as diffuse idiopathic neuroendocrine cell hyperplasia and with lymphoreticular malignancies complicated by

paraneoplastic pemphigus [5,10]. This review focuses on exposure-related bronchiolitis, beginning with the histologic spectrum of bronchiolitis, followed by an update on causes and exposure settings, diagnosis including newer diagnostic modalities, and approaches to disease management.

^aDivision of Environmental and Occupational Health Sciences, National Jewish Health, Denver, ^bDivision of Pulmonary Sciences and Critical Care Medicine, University of Colorado School of Medicine, ^cDepartment of Environmental and Occupational Health, Colorado School of Public Health, ^dDepartment of Pathology, University of Colorado Anschutz Medical Campus, Aurora and ^eDivision of Pathology, National Jewish Health, Denver, Colorado, USA

Correspondence to Silpa D. Krefft, MD, MPH, Division of Environmental and Occupational Health Sciences, National Jewish Health, 1400 Jackson Street, G208, Denver, CO 80206, USA. Tel: +1 303 398 1867; fax: +1 303 398 1452; e-mail: KrefftS@NJHealth.org

Curr Opin Allergy Clin Immunol 2018, 18:87–95

DOI:10.1097/ACI.0000000000000425

KEY POINTS

- No specific histopathologic pattern of bronchiolitis is pathognomonic for exposure-related bronchiolitis as one or more histologic patterns may be present.
- A high index of suspicion is needed to identify relevant exposures and for diagnosis of occupational bronchiolitis, as conventional diagnostic tools often yield findings that are nonspecific or normal.
- Recent advances that may aid in diagnosis of occupational bronchiolitis include transbronchial cryobiopsy, lung clearance index testing, and impulse oscillometry, although further research is needed.

HISTOPATHOLOGIC SPECTRUM OF BRONCHIOLITIS

The most concise definition of bronchiolitis is inflammation of the small airways that are 2 mm or less in diameter. Bronchiolitis occurs as a response to tissue injury, with inflammation of small airway epithelial cells and subepithelial structures leading to excessive fibroproliferation due to aberrant tissue repair [1]. Primary bronchiolar disorders – those in which the pathologic process centers mainly on noncartilaginous small airways – are distinguished from disorders such as asthma, hypersensitivity pneumonitis, and other large airway or interstitial lung diseases in which secondary bronchiolar abnormalities often occur [11]. The major histopathologic types of bronchiolitis are constrictive, obliterative, proliferative, lymphocytic, and respiratory bronchiolitis along with mineral dust airway disease [1,3]. The full spectrum of these histopathologic patterns may be seen in exposure-related bronchiolitis.

Constrictive bronchiolitis

Constrictive bronchiolitis occurs from airway luminal narrowing by concentric subepithelial deposition of collagen in the bronchiolar wall. This inflammatory process surrounds rather than fills the bronchiolar lumen, resulting in extrinsic compression of the small airway. Constrictive bronchiolitis can be difficult to observe on routine hematoxylin and eosin (H & E) stains, and special elastic tissue stains, such as pentachrome stains, are helpful in assessing the degree of small airway constriction (Fig. 1a and b). The fibrosis may be accompanied by varying degrees of inflammation, usually lymphocytic. Constrictive bronchiolitis has been described in nearly all of the clinical categories of bronchiolitis, and is one of the classic sequelae of acute and chronic inhalational injury.

Obliterative bronchiolitis

Also referred to as bronchiolitis obliterans, obliterative bronchiolitis is characterized by total or near total obliteration of the small airway by fibrosis, usually with minimal inflammation. The fibrosis consists predominantly of mature collagen. Obliterated airways can be difficult to appreciate on H & E stains (Fig. 2a), and often elastic tissue and collagen stains are necessary to identify the obliterated airway (Fig. 2b). Identification can be even more difficult because the lesion is patchy – not all airways are affected. Frequently, there are also airways with some degree of constrictive bronchiolitis. A helpful clue to the presence of obliterated airways is the finding of unaccompanied pulmonary arteries, as pulmonary arteries and airways travel together in the bronchovascular bundle.

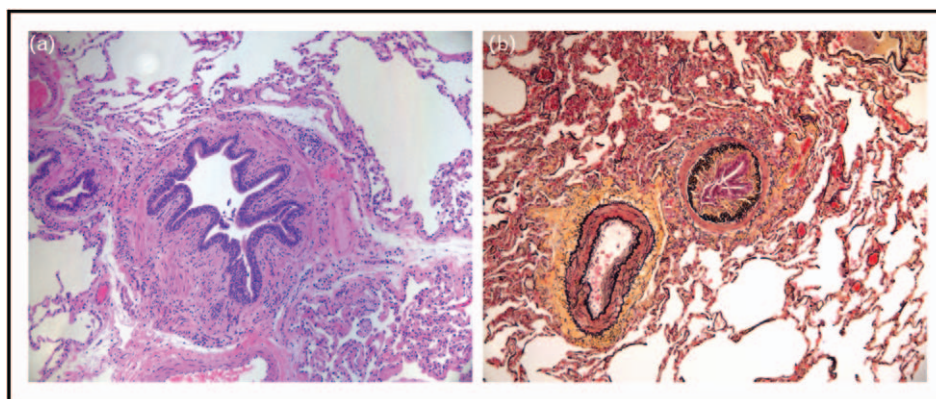


FIGURE 1. (a) H & E stained image of an airway shows mild constrictive changes characterized by pink fibrous tissue between the smooth muscle and the bronchiolar epithelium. (b) Low-power image of an airway and adjacent pulmonary artery stained with pentachrome. The constricted airway shows circumferential deposition of yellow collagen interposed between the elastic lamina (black) and the basement membrane of the epithelium (purple). The adjacent pulmonary artery is easily identified by the presence of double elastic laminae.

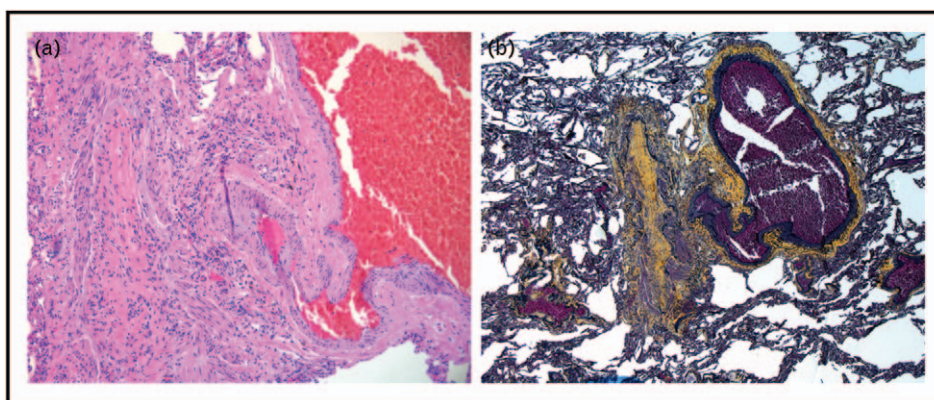


FIGURE 2. (a) H & E image of an obliterated airway. Here, one can appreciate the difficulty is looking for a totally obliterated airway. The pink central fibrosis is the scarred lumen and on this higher power image, the smooth muscle layer of the bronchiolar wall is evident. The adjacent pulmonary artery (with the intraluminal red blood cells) aids in establishing the bronchovascular location. (b) Low-power image of the same artery and bronchiole as in panel (a), but with a pentachrome stain, illustrates the luminal filling of the airway by dense collagen (yellow). The airway is much easier to identify with this staining technique as the elastic lamina is highlighted in black and the smooth muscle in red-purple.

Proliferative bronchiolitis (organizing pneumonia)

Organizing pneumonia (formerly, bronchiolitis obliterans organizing pneumonia, BOOP) is the primary form of proliferative bronchiolitis. The histology is characterized by intraluminal buds or plugs of fibroblastic tissue (also called Masson bodies). Unlike obliterative or constrictive bronchiolitis, organizing pneumonia is located within airway lumina and can extend into adjacent airways in a serpiginous pattern. The fibroblasts have a spindled lower power appearance with parallel arrays and a pale-staining matrix. The pentachrome (Movat) stain effectively highlights immature collagen with a blue to blue-green hue (mature collagen stains yellow) (Fig. 3). Often, foamy macrophages are identified in adjacent airspaces. Another feature of organizing pneumonia is the presence of small blood vessels.

Lymphocytic bronchiolitis

Lymphocytic bronchiolitis shares features of lymphoid hyperplasia with follicular bronchiolitis, and both typically occur in response to an immune stimulus. Lymphocytic bronchiolitis shows a band-like inflammatory infiltrate in the bronchiolar submucosa composed of a mixture of mature B and T lymphocytes (Fig. 4a). Follicular bronchiolitis is also composed of a mixture of B and T lymphocytes; however, lymphocytes are aggregated into follicles and often show germinal center formation (Fig. 4b). Lymphocytic and follicular bronchiolitis can completely encase the small airway, and with

follicular bronchiolitis, there can be compression of the bronchiolar lumen. A distinctive pattern of lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia has been described in nylon flocking industry workers, in which inhalation of short lengths of synthetic fibers stimulates an immunologic response and can lead to disabling occupational lung disease termed ‘nylon flock worker’s lung’ [12].

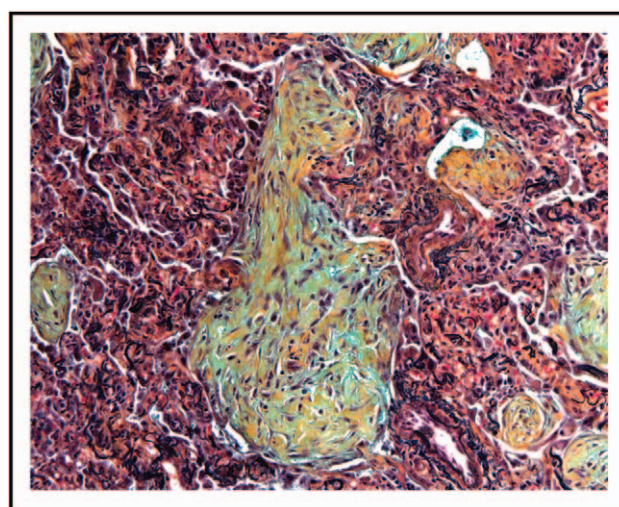


FIGURE 3. Pentachrome stains of organizing pneumonia. The plug of organizing fibroblastic/myofibroblastic tissue, which stains green because of the mucopolysaccharide content, fills the lumen. Adjacent airspaces also contain plugs of organizing pneumonia. Adjacent alveolar septae are mildly expanded by chronic inflammation, but no significant fibrosis is identified.

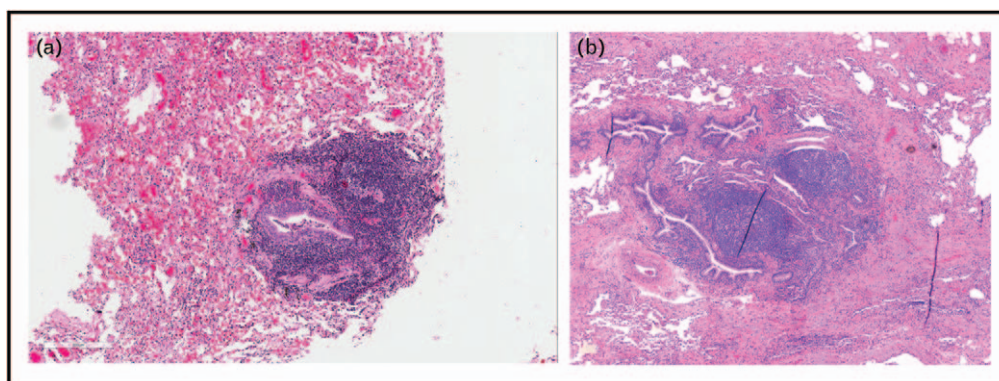


FIGURE 4. (a) Image of lymphocytic bronchiolitis shows a dense infiltrate of mature lymphocytes partially surrounding an airway (H & E stain). (b) In contrast to lymphocytic bronchiolitis, follicular bronchiolitis demonstrates lymphoid follicles with germinal centers. These follicles partially surround and focally compress the airway lumen (H & E stain).

Respiratory bronchiolitis

Respiratory bronchiolitis has a distinct appearance characterized by loose accumulations of finely granular, yellow-brown pigmented macrophages within membranous and respiratory bronchioles (Fig. 5). The macrophages often extend into adjacent alveolar spaces and are mixed with mucin. There is usually an accompanying peribronchiolar metaplastic change of the alveolar spaces, imparting an irregular appearance to the bronchiole. The pigment stains dusky blue on iron stain, which aids in differentiating smoking pigment from the coarser granules of hemosiderin.

Mineral dust airway disease

The term mineral dust airway disease refers to the deposition of inhaled inorganic dust in the small

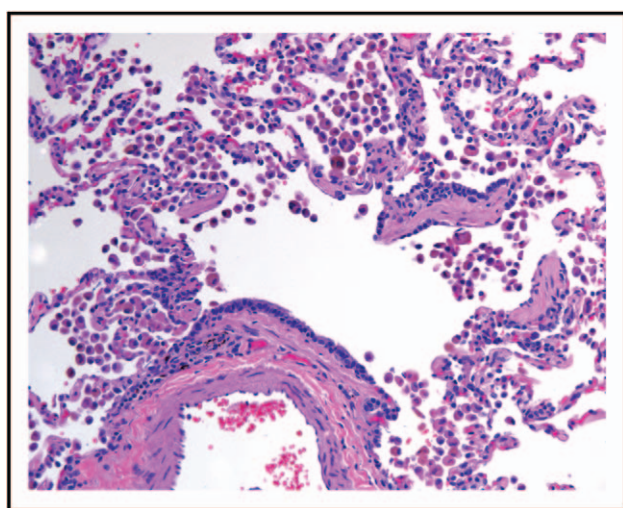


FIGURE 5. Yellow-brown pigmented macrophages (smoker's macrophages) of respiratory bronchiolitis accumulate within membranous and respiratory bronchioles, with focal extension into surrounding airspaces (H & E stain).

airways (Fig. 6a and b), leading to chronic inflammation with associated fibrosis [13]. The degree of bronchiolar wall fibrosis is linked to local dust burden and can be associated with obstructive lung function abnormalities. Exposure to a number of inorganic dusts including asbestos, coal mine dust, silica, silicates, talc, and aluminum oxide has been associated with this form of bronchiolitis [14[■]].

CAUSES AND EXPOSURE SETTINGS

Acute toxic inhalation was, until fairly recently, the most widely recognized exposure circumstance for occupational bronchiolitis. The earliest case reports of occupational bronchiolitis were associated with acute exposure to poisonous gases containing hydrogen sulfide, sulfur dioxide, and chlorine during World War I (1914–1918), and later to sulfur mustard in the Iran–Iraq War (1980–1988) (Table 1). These toxic gases caused acute lung injury with rapid onset of chemical pneumonitis and pulmonary edema. In survivors, respiratory impairment was often severe [15,16]. Reports have described acute pneumonitis followed by progressive fixed airways obstruction due to obliterative/constrictive bronchiolitis in workers exposed to nitrogen oxides and other toxic fermentation gases during grain silo loading/unloading – so-called silo filler's disease [17]. Bronchiolitis from acute exposure to other irritants including ammonia, phosgene, cadmium, and household cleaners has also been reported [18–20].

Chronic inhalational exposures associated with insidious presentation of bronchiolitis have emerged as major concerns over the past 2 decades (Table 1). Much of what is currently known comes from research on diacetyl-exposed workers in flavor manufacturing, flavor chemical production, and in a variety of food flavoring industries including snack foods (e.g., microwave popcorn manufacturing,

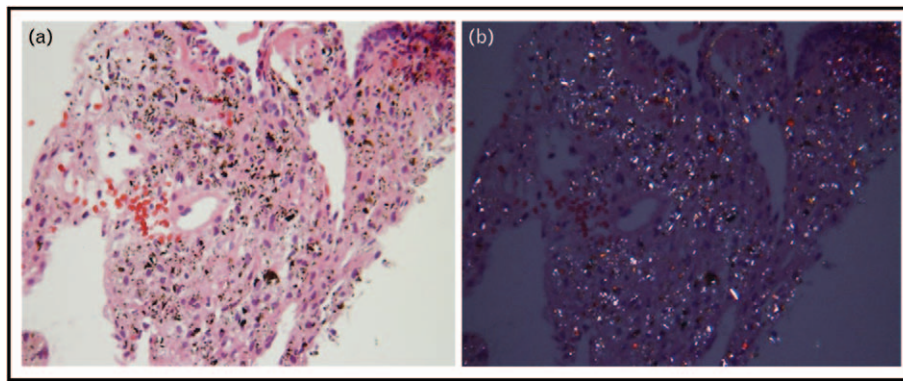


FIGURE 6. (a) H & E stained section demonstrates peribronchiolar fibrosis associated with dust-laden macrophages. The airway epithelium is visible in the upper right of the image and shows normal respiratory type epithelium. (b) Examination of the tissue under polarized light reveals numerous refractile silicates, which can be seen with exposure to dusts containing crystalline silica.

chips, confections, and baked products), dairy products, and coffee roasting [21–23]. A seminal investigation by the National Institute for Occupational Safety and Health (NIOSH) found that 87% of 135 workers at a microwave popcorn production plant using diacetyl for butter flavoring had excessive rates of respiratory symptoms, frequent physician-diagnosed obstructive lung disease, and fixed airways obstruction on spirometry [24]. In-depth clinical description of eight former workers from this facility described findings of occupational bronchiolitis [25].

A 2011 case series of 80 soldiers who had served since 2001 in Iraq or Afghanistan described persistent respiratory symptoms (mainly exertional dyspnea) in those reporting inhalational exposures to sandstorms, combustion products from burn pits in which waste was burned with diesel fuel, combat dusts, and/or exposure to a sulfur mine fire from which sulfur oxides were released. Surgical lung biopsies in 38 symptomatic soldiers showed findings of obliterative and constrictive bronchiolitis, with

luminal narrowing and peribronchial pigment [26]. Other investigators have reported similar findings in post-9/11 military personnel who have deployed to Iraq, Afghanistan, and other southwest Asia locations (deployers) [27].

Cases of exposure-related bronchiolitis have occurred among World Trade Center (WTC) responders who were exposed to large clouds of dust at ‘Ground Zero’ following the collapse of the WTC on 11 September 2001 [28,29]. For months thereafter, smoldering fires burned, diesel fumes were released, and alkaline WTC dust was aerosolized until recovery efforts ended on 30 May 2002 [30]. One report described a police officer who worked for 16-h shifts, 7 days a week for 3 weeks after the disaster. Within 2 days he noted onset of dyspnea associated with a progressive decline in lung function. Surgical lung biopsy showed focal obliterative bronchiolitis with rare nonnecrotizing granulomas [31].

Case reports describe a number of additional exposures associated with risk for indolent bronchiolitis

Table 1. Exposures and reported histopathologic patterns of occupational bronchiolitis

Exposures	Histopathology
Silo fillers disease (nitrogen oxides)	Constrictive bronchiolitis
Sulfur mustard gas	Constrictive, lymphocytic, and respiratory bronchiolitis
Nylon flocking industry workers	Lymphocytic bronchiolitis
Flavoring-related lung disease (e.g., diacetyl)	Constrictive and obliterative bronchiolitis
World Trade Center-related lung disease	Chronic bronchiolitis and focal obliterative bronchiolitis
Post-9/11 deployment-related bronchiolitis	Constrictive, obliterative, proliferative, lymphocytic, and respiratory bronchiolitis
Mineral dust (coal mine dust, silica/silicates, asbestos, talc, aluminum oxide)	Respiratory bronchiolitis

including a worker with long-term exposure to cotton dust [32]; a case of BOOP in a worker with 3 months of workplace exposure to heated polyester powders containing titanium dioxide nanoparticles [33]; fly ash [34] and from styrene exposure in fiberglass boatbuilders [35]. Possible small airway effects from nanoparticle exposures and from inhalation of components of electronic nicotine delivery systems await further investigation.

DIAGNOSIS AND NEWER DIAGNOSTIC MODALITIES

Diagnosis of bronchiolitis with noninvasive methods may be challenging unless there is substantial lung involvement. These challenges are related to the distal and often patchy inflammation affecting the large surface area of small airways. A strong index of suspicion in the appropriate clinical setting in combination with suggestive physiologic and chest imaging abnormalities may aid in diagnosing bronchiolitis. However, physiologic and imaging abnormalities are not always present and, in some cases, histopathologic assessment is needed for diagnosis [29,36,37,38[•]].

Clinical presentation

The severe respiratory symptoms associated with pulmonary edema following acute toxic gas inhalation are not delayed or subtle. In survivors, there is often a period of apparent recovery, followed within days to weeks by progressive dyspnea, chest tightness, and cough associated with lung function decline from evolving bronchiolitis. The clinical presentation of patients with indolent exposure-related bronchiolitis is characterized by insidious onset and progressively worsening dyspnea on exertion, often with nonproductive cough. Patients typically describe no work-related pattern of symptom onset or exacerbation. The latency period for symptom onset in indolent bronchiolitis varies from weeks to years, with a median symptom latency in microwave popcorn workers of 1.5 years (range 5 months to 9 years).

Comprehensive medical and occupational/environmental exposure history

Clinicians should conduct a thorough review of a symptomatic patient's medical and social history as well as a comprehensive history of occupational and environmental exposures. Review of the patient's chronology of past jobs, job titles, and job tasks is necessary to elicit details of exposure to dusts, gases, fumes, and other toxicants [38[•],39]. Information on

use of respiratory protection and on similar symptoms or lung conditions affecting coworkers should be elicited.

Pulmonary function testing

Lung function in bronchiolitis is associated classically with obstruction characterized by reduced forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC) ratio, usually with no significant response to bronchodilator [1,3,37]. Lung volumes may show air trapping based on increased residual volume. Restrictive abnormalities (characterized by reduced FVC, FVC, and normal or increased FEV1/FVC ratio) as well as mixed restrictive/obstructive and normal spirometry have been described in cases of constrictive bronchiolitis [26,40].

Spirometry has been found insensitive in bronchiolitis diagnosis in a number of studies [26,37,38[•],40,41]. Post-9/11 military southwest Asia and Afghanistan deployers with biopsy-proven bronchiolitis were more likely to have decreased diffusion capacity for carbon monoxide and low predicted maximal oxygen consumption on cardiopulmonary exercise testing than abnormal spirometry [27]. The extent to which oxygenation is impaired from occupational bronchiolitis is variable, probably due to variability in extent of affected small airways.

Chest imaging

Chest radiography in indolent occupational bronchiolitis is usually normal or shows nonspecific hyperinflation and bronchial wall thickening. High-resolution chest computed tomography (HRCT) findings of bronchial wall thickening, tree-in-bud opacities, centrilobular nodules, and mosaic attenuation are disease hallmarks, though are often subtle [42,43]. In particular, mosaic attenuation has been associated with bronchiolitis obliterans [44,45]. Expiratory imaging is needed to optimally evaluate for air trapping/mosaicism [46]. Notably, biopsy-proven bronchiolitis in the absence of HRCT abnormalities has been described in multiple studies [26,37,40,47[•]].

Lung biopsy

Because of the subtle and often patchy histologic findings of bronchiolitis, transbronchial lung biopsy is usually inadequate for diagnosis. Video-assisted thoracoscopic surgical (VATS) lung biopsy may be indicated in the diagnostic evaluation of bronchiolitis, especially in the setting of exposed patients with unexplained respiratory symptoms

with normal or nondiagnostic physiology and chest imaging, and when symptoms are disabling, lung function is declining, and/or treatment has failed [36,37,38].

Although surgical lung biopsy may be important for diagnostic clarity, concerns about risk have prompted efforts to find less invasive methods for accurate diagnosis. Transbronchial cryobiopsy is a new method that yields lung specimens comparable in size to specimens obtained via VATS biopsy. Transbronchial cryobiopsy has been used in evaluation of patients with interstitial lung disease and was helpful in establishing a diagnosis of deployment-related constrictive bronchiolitis in one case [48,49]. Widespread adoption of transbronchial cryobiopsy has been hindered by higher risks of bleeding and pneumothorax than traditional bronchoscopy [50–52]. Furthermore, given limitations of a transbronchial approach, pleura is not sampled and respiratory bronchioles may not be adequately sampled. Further research is needed to assess utility of transbronchial cryobiopsy in evaluation of bronchiolitis.

Lung clearance index testing and impulse oscillometry

There is increasing interest in investigating the utility of the lung clearance index (LCI) and impulse oscillometry (IOS) as noninvasive markers of small airways disease [47,53,54].

LCI testing uses a multiple breath nitrogen washout technique to assess lung ventilation inhomogeneity. Testing begins with tidal breathing of room air followed by washout until the tracer gas (nitrogen or sulfur hexafluoride) reaches less than 2.5% of initial concentration. LCI scores are reported as a mean of two or three trials, with testing sessions in adults lasting 30–60 min [55]. LCI has been studied as a marker of early small airways injury in cystic fibrosis. These studies show that LCI is a sensitive and often superior method to spirometry in detection of small airways abnormalities [56–58]. A study of participants with bronchiolitis obliterans compared with healthy controls demonstrated a significant difference in LCI scores [54]. In military deployers with small airways disease, there was higher agreement between abnormally increased LCI score and abnormal lung biopsy than with rest and exercise lung function testing [47]. LCI may have applications in longitudinal disease monitoring. In one study, LCI scores obtained 3 years before chest computed tomography (CT) scans correlated with presence or absence of CT abnormalities better than FEV1 [59]. LCI is not effort dependent [55,60,61]. Its main disadvantages

are that testing requires special equipment and training and takes longer than spirometry [55].

IOS, a technique that uses forced oscillations to measure airways resistance and reactance, has detected abnormalities suggestive for small airways disease in WTC-exposed workers; verification of these findings is needed in larger populations [53,62]. Like spirometry, IOS is performed quickly and has the added benefit of effort independence. Individuals who have difficulty with spirometry often find IOS easier to perform [63]. IOS is used clinically but has not been widely adopted as a clinical test of small airways disease. Further research on the utility of LCI and IOS is needed to determine whether these tests improve the diagnosis of small airways abnormalities.

TREATMENT, PROGNOSIS, AND PREVENTION

Treatment of acute exposure-related lung injury with systemic corticosteroids is associated with reduced incidence of later-stage bronchiolitis [64]. There is no known treatment to reverse indolent occupational bronchiolitis. A few studies, primarily in cohorts of sulfur mustard-exposed individuals, examined the therapeutic role of inhaled and systemic steroids, *n*-acetylcysteine, and macrolides [3,15]. There is variable evidence of improvement in lung function with these therapies [65], and further research using controlled clinical trials is needed. The role of immunomodulatory medications in stabilizing lung function decline in patients with bronchiolitis remains uncertain. In nine affected microwave popcorn workers, treatment with oral corticosteroids in seven and with oral steroids and cyclophosphamide in two did not improve lung function [25]. In severe or progressive cases of bronchiolitis, patients may need treatment with supplemental oxygen and/or referral for lung transplantation [3,24].

Prognosis in indolent occupational bronchiolitis appears more favorable than the relentless downhill course characteristic of posttransplant and autoimmune bronchiolitis. Among flavoring-exposed workers, incidence and severity of obstructive abnormalities is associated with increasing cumulative exposure to diacetyl and disease progression to continued exposure [66]. Exposure cessation typically results in stabilization of lung function [25,67]. Increased lung disease mortality was found at a microwave popcorn production facility, mainly among workers employed before the company reduced diacetyl exposure [68]. Although less is known about prognosis in other types of exposure-related bronchiolitis, these findings suggest

that, for most patients with occupational bronchiolitis, exposure removal is essential.

Management of those with workplace exposure to agents that cause bronchiolitis involves appropriate medical surveillance, including high-quality lung function testing and plans for diagnostic referral and exposure removal in those with suspected bronchiolitis. NIOSH recommends medical surveillance at least every 6 months for diacetyl-exposed workers [69]. Workplace exposure monitoring should be coordinated with medical surveillance, and workers in high-exposure job duties followed regularly for symptoms and spirometric abnormalities. Control of occupational bronchiolitis requires both early detection of abnormal spirometry and regular medical monitoring to detect accelerated decline in spirometry over time.

CONCLUSION

Exposure-related bronchiolitis, especially in its indolent form, is an increasingly important clinical problem with a spectrum of histopathologic abnormalities. A high index of clinical suspicion, early recognition, accurate diagnosis, and exposure removal are essential.

Acknowledgements

Photomicrograph of mineral dust airway disease kindly provided by Dr E.L. Petsonk, Professor of Medicine, West Virginia University School of Medicine.

Financial support and sponsorship

C.S.R., S.D.K., and National Jewish Health have received research funding from the Department of Defense (DoD). Their research includes evaluation of noninvasive markers of post-9/11 deployment-related lung diseases in DoD grant 'Mechanisms and Treatment of Deployment-Related Lung Injury: Repair of the Injured Epithelium'. C.S.R. is the principal investigator of Health Resources and Services Administration (HRSA) grant titled 'Black Lung Clinics Program' as well as coinvestigator of Alpha Foundation for Improvement of Mine Safety and Health grant titled 'Linkage of Active Miner Surveillance, Former Miner Disability Evaluations, and Mortality Data Sets to Evaluate and Prevent Lifetime Risk of Cardiopulmonary Disease in US Miners'. In addition to the funding sources listed above, S.D.K. was supported by grant T42OH009229 funded by the Centers for Disease Control and Prevention for the study 'Utility of Lung Clearance Index Score as a Noninvasive Marker of Deployment Lung Disease' with additional support from the Sergeant Sullivan Center. The contents of the article are solely the responsibility of the authors and do not necessarily represent the official views of the

Centers for Disease Controls and Prevention or the Department of Health and Human Services.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med* 2014; 370:1820–1828.
2. Cha SI, Shin KM, Kim M, *et al.* Mycoplasma pneumoniae bronchiolitis in adults: clinicoradiologic features and clinical course. *Scand J Infect Dis* 2009; 41:515–519.
3. Garibaldi BT, Illei P, Danoff SK. Bronchiolitis. *Immunol Allergy Clin North Am* 2012; 32:601–619.
4. Iwata M, Colby TV, Kitaichi M. Diffuse panbronchiolitis: diagnosis and distinction from various pulmonary diseases with centrilobular interstitial foam cell accumulations. *Hum Pathol* 1994; 25:357–363.
5. King TE Jr. Miscellaneous causes of bronchiolitis: inhalational, infectious, drug-induced, and idiopathic. *Semin Respir Crit Care Med* 2003; 24:567–576.
6. Kudoh S, Keicho N. Diffuse panbronchiolitis. *Clin Chest Med* 2012; 33:297–305.
7. Ryu JH. Classification and approach to bronchiolar diseases. *Curr Opin Pulm Med* 2006; 12:145–151.
8. Shen T, Braude S. Obliterative bronchiolitis after rituximab administration: a new manifestation of rituximab-associated pulmonary toxicity. *Intern Med J* 2012; 42:597–599.
9. Vassallo R, Ryu JH. Smoking-related interstitial lung diseases. *Clin Chest Med* 2012; 33:165–178.
10. Nousari HC, Deterding R, Wojtczak H, *et al.* The mechanism of respiratory failure in paraneoplastic pemphigus. *N Engl J Med* 1999; 340:1406–1410.
11. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med* 2003; 168:1277–1292.
12. Boag AH, Colby TV, Fraire AE, *et al.* The pathology of interstitial lung disease in nylon flock workers. *Am J Surg Pathol* 1999; 23:1539–1545.
13. Churg A, Wright JL, Wiggs B, *et al.* Small airways disease and mineral dust exposure. Prevalence, structure, and function. *Am Rev Respir Dis* 1985; 131:139–143.
14. Petsonk EL, Stansbury RC, Beeckman-Wagner LA, *et al.* Small airway dysfunction and abnormal exercise responses. A study in Coal Miners. *Ann Am Thorac Soc* 2016; 13:1076–1080.
- A recent analysis of small airways dysfunction in workers exposed to coal mine dust shows that these abnormalities may be associated with ventilatory abnormalities on cardiopulmonary exercise testing, providing insight into causes of exercise intolerance.
15. Ghanei M, Abolmaali K, Aslani J. Efficacy of concomitant administration of clarithromycin and acetylcysteine in bronchiolitis obliterans in seventeen sulfur mustard-exposed patients: an open-label study. *Curr Ther Res Clin Exp* 2004; 65:495–504.
16. Khateri S, Ghanei M, Keshavarz S, *et al.* Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. *J Occup Environ Med* 2003; 45:1136–1143.
17. Douglas WW, Hepper NG, Colby TV. Silo-filler's disease. *Mayo Clin Proc* 1989; 64:291–304.
18. Figueiredo S, Morais A, Magalhães A, *et al.* Occupational constrictive bronchiolitis with normal physical, functional and image findings. *Rev Port Pneumol* 2009; 15:729–732.
19. Fuehrer NE, Marchevsky AM, Jagirdar J. Presence of c-KIT-positive mast cells in obliterative bronchiolitis from diverse causes. *Arch Pathol Lab Med* 2009; 133:1420–1425.
20. Visscher DW, Myers JL. Bronchiolitis: the pathologist's perspective. *Proc Am Thorac Soc* 2006; 3:41–47.
21. Bailey RL, Cox-Ganser JM, Duling MG, *et al.* Respiratory morbidity in a coffee processing workplace with sentinel obliterative bronchiolitis cases. *Am J Ind Med* 2015; 58:1235–1245.
22. Cavalcanti Zdo R, Albuquerque Filho AP, Pereira CA, Coletta EN. Bronchiolitis associated with exposure to artificial butter flavoring in workers at a cookie factory in Brazil. *J Bras Pneumol* 2012; 38:395–399.
23. Day G, LeBouf R, Grote A, *et al.* Identification and measurement of diacetyl substitutes in dry bakery mix production. *J Occup Environ Hyg* 2011; 8:93–103.
24. Kreiss K, Gomaa A, Kullman G, *et al.* Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med* 2002; 347:330–338.

25. Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J* 2004; 24:298–302.
26. King MS, Eisenberg R, Newman JH, *et al.* Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med* 2011; 365:222–230.
27. Dhome S, Gottschall B, Robinson M, *et al.* Lung disease in deployers returning from Afghanistan and Iraq. B106 Occupational and Environmental Determinants of Lung Function; 2013. p. A3669-A.
28. de la Hoz RE, Christie J, Teamer JA, *et al.* Reflux symptoms and disorders and pulmonary disease in former World Trade Center rescue and recovery workers and volunteers. *J Occup Environ Med* 2008; 50:1351–1354.
29. Wu M, Gordon RE, Herbert R, *et al.* Case report: lung disease in World Trade Center responders exposed to dust and smoke: carbon nanotubes found in the lungs of World Trade Center patients and dust samples. *Environ Health Perspect* 2010; 118:499–504.
30. Guidotti TL, Prezant D, de la Hoz RE, Miller A. The evolving spectrum of pulmonary disease in responders to the World Trade Center tragedy. *Am J Ind Med* 2011; 54:649–660.
31. Mann JM, Sha KK, Kline G, *et al.* World Trade Center dyspnea: bronchiolitis obliterans with functional improvement: a case report. *Am J Ind Med* 2005; 48:225–229.
32. Mittal R, Gupta P, Chhabra SK. Occupational bronchiolitis induced by cotton dust exposure in a nonsmoker. *Indian J Occup Environ Med* 2016; 20:118–120.
33. Cheng TH, Ko FC, Chang JL, Wu KA. Bronchiolitis obliterans organizing pneumonia due to titanium nanoparticles in paint. *Ann Thorac Surg* 2012; 93:666–669.
34. Boswell RT, McCunney RJ. Bronchiolitis obliterans from exposure to incinerator fly ash. *J Occup Environ Med* 1995; 37:850–855.
35. Janigan DT, Kilp T, Michael R, McCleave JJ. Bronchiolitis obliterans in a man who used his wood-burning stove to burn synthetic construction materials. *CMAJ* 1997; 156:1171–1173.
36. Krefft SD, Meehan R, Rose CS. Emerging spectrum of deployment-related respiratory diseases. *Curr Opin Pulm Med* 2015; 21:185–192.
37. Kreiss K. Occupational causes of constrictive bronchiolitis. *Curr Opin Allergy Clin Immunol* 2013; 13:167–172.
38. Rose CS. Early detection, clinical diagnosis, and management of lung disease ■ from exposure to diacetyl. *Toxicology* 2017; 388:9–14.
- The recent overview provides a summary of approaches to clinical diagnosis and management of lung diseases including bronchiolitis in workers exposed to diacetyl.
39. Sauler M, Gulati M. Newly recognized occupational and environmental causes of chronic terminal airways and parenchymal lung disease. *Clin Chest Med* 2012; 33:667–680.
40. Ghanei M, Tazelaar HD, Chilosi M, *et al.* An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients. *Respir Med* 2008; 102:825–830.
41. Markopoulou KD, Cool CD, Elliot TL, *et al.* Obliterative bronchiolitis: varying presentations and clinicopathological correlation. *Eur Respir J* 2002; 19:20–30.
42. Devakonda A, Raoof S, Sung A, *et al.* Bronchiolar disorders: a clinical-radiological diagnostic algorithm. *Chest* 2010; 137:938–951.
43. van Rooy FG, Rooyackers JM, Prokop M, *et al.* Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med* 2007; 176:498–504.
44. Jensen SP, Lynch DA, Brown KK, *et al.* High-resolution CT features of severe asthma and bronchiolitis obliterans. *Clin Radiol* 2002; 57:1078–1085.
45. Lynch DA. Imaging of small airways disease and chronic obstructive pulmonary disease. *Clin Chest Med* 2008; 29:165–179; vii.
46. Pipavath SJ, Lynch DA, Cool C, *et al.* Radiologic and pathologic features of bronchiolitis. *AJR Am J Roentgenol* 2005; 185:354–363.
47. Krefft SD, Strand M, Smith J, *et al.* Utility of lung clearance index testing as a ■ noninvasive marker of deployment-related lung disease. *J Occup Environ Med* 2017; 59:707–711.
- The study shows that lung clearance index (LCI) testing may be an important adjunct in the noninvasive clinical diagnosis of symptomatic military personnel with biopsy-proven deployment-related bronchiolitis.
48. Kropski JA, Pritchett JM, Mason WR, *et al.* Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PLoS One* 2013; 8:e78674.
49. Lentz RJ, Fessel JP, Johnson JE, *et al.* Transbronchial cryobiopsy can ■ diagnose constrictive bronchiolitis in veterans of recent conflicts in the Middle East. *Am J Respir Crit Care Med* 2016; 193:806–808.
- The case report provides support for the use of transbronchial cryobiopsy in the diagnosis of military deployers with constrictive bronchiolitis.
50. López V, López X, Herrero S, *et al.* Complications of transbronchial cryobiopsy in interstitial lung diseases. *Eur Respir J* 2015; 46(Suppl 59):A2194.
51. Ramaswamy A, Homer R, Killam J, *et al.* Comparison of transbronchial and cryobiopsies in evaluation of diffuse parenchymal lung disease. *J Bronchology Interv Pulmonol* 2016; 23:14–21.
52. Stahl DL, Richard KM, Papadimos TJ. Complications of bronchoscopy: a concise synopsis. *Int J Crit Illn Inj Sci* 2015; 5:189–195.
53. Friedman SM, Maslow CB, Reibman J, *et al.* Case-control study of lung function in World Trade Center Health Registry area residents and workers. *Am J Respir Crit Care Med* 2011; 184:582–589.
54. Rosewich M, Michel F, Filate-Belachew N, *et al.* Lung clearance index in ■ patients with bronchiolitis obliterans. *Eur Respir J* 2016; 48(Suppl 60):A1604.
- The proof of concept study of LCI testing shows significant differences in LCI scores in patients with bronchiolitis obliterans compared with health controls.
55. Horsley A. Lung clearance index in the assessment of airways disease. *Respir Med* 2009; 103:793–799.
56. Ellemunter H, Fuchs SI, Unsinn KM, *et al.* Sensitivity of lung clearance index and chest computed tomography in early CF lung disease. *Respir Med* 2010; 104:1834–1842.
57. Horsley AR, Gustafsson PM, Macleod KA, *et al.* Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. *Thorax* 2008; 63:135–140.
58. Kent L, Reix P, Innes JA, *et al.* Lung clearance index: evidence for use in clinical trials in cystic fibrosis. *J Cyst Fibros* 2014; 13:123–138.
59. Fuchs SI, Gappa M, Eder J, *et al.* Tracking lung clearance index and chest CT in mild cystic fibrosis lung disease over a period of three years. *Respir Med* 2014; 108:865–874.
60. Fuchs S, Petri E, Hülskamp G, Gappa M. Routine measurement of the LCI in CF with an ultrasonic device for multiple breath nitrogen washout. *Eur Respir J* 2012; 40(Suppl 56):P4601.
61. Fuchs SI, Eder J, Ellemunter H, Gappa M. Lung clearance index: normal values, repeatability, and reproducibility in healthy children and adolescents. *Pediatr Pulmonol* 2009; 44:1180–1185.
62. Bickel SG, Morton RL, O'Hagan A, Eid N. A unique signature of disease: impulse oscillometry findings in constrictive bronchiolitis. C75. Improving and Assessing Respiratory Function. 2016. p. A5951-A.
63. Desiraju K, Agrawal A. Impulse oscillometry: the state-of-art for lung function testing. *Lung India* 2016; 33:410–416.
64. [No authors listed]. Respiratory health hazards in agriculture. *Am J Respir Crit Care Med* 1998; 158(5 Pt 2):S1–S76.
65. Abtahi H, Peiman S, Foroumandi M, Safavi E. Long term follow-up of sulfur ■ mustard related bronchiolitis obliterans treatment. *Acta Med Iran* 2016; 54:605–609.
- One of the few published articles on treatment of exposure-related bronchiolitis from sulfur mustard inhalation.
66. Centers for Disease Control and Prevention (CDC). Fixed obstructive lung disease in workers at a microwave popcorn factory – Missouri, 2000–2002. *MMWR Morb Mortal Wkly Rep* 2002; 51:345–347.
67. Kanwal R, Kullman G, Fedan KB, Kreiss K. Occupational lung disease risk and exposure to butter-flavoring chemicals after implementation of controls at a microwave popcorn plant. *Public Health Rep* 2011; 126:480–494.
68. Halldin CN, Suarathana E, Fedan KB, *et al.* Increased respiratory disease mortality at a microwave popcorn production facility with worker risk of bronchiolitis obliterans. *PLoS One* 2013; 8:e57935.
69. Weissman DN. Medical surveillance for the emerging occupational and environmental respiratory diseases. *Curr Opin Allergy Clin Immunol* 2014; 14:119–125.