Occupational Bronchiolitis
An Update

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KEYWORDS

• Constrictive bronchiolitis • Military deployment • Obliterative bronchiolitis • Flavoring • Diacetyl • 2,3-Pentanedione • Styrene

KEY POINTS

- Workers in industries producing or using flavoring containing diacetyl or 2,3-pentanedione continue to be at risk for flavoring-related lung disease, although the disease is preventable.
- Cases of constrictive bronchiolitis have been associated with military deployments to Iraq and Afghanistan, but the causative exposure(s) have not been identified.
- Multiple reports in recent years have drawn attention to previously unrecognized risk factors for occupational bronchiolitis following exposures in several settings, such as fiberglass-reinforced plastic boatbuilding.

INTRODUCTION

Bronchiolitis is characterized by inflammation of the small airways (<2 mm).[1,2] The most common clinical presentation includes insidious onset of exertional dyspnea and cough. The complexities surrounding occupational bronchiolitis are many. At the forefront of those complexities is the terminology used to describe the wide range of pathologies and causative exposures that fall under the umbrella term occupational bronchiolitis (eg, bronchiolitis obliterans, constrictive bronchiolitis, obliterative bronchiolitis, proliferative bronchiolitis, popcorn lung disease). Consequently, small airways diseases resulting from occupational exposures are often defined by pathologic description[3]; however, most workers suspected of having occupational bronchiolitis do not undergo biopsy.[4] Thus, the most commonly used naming scheme is left open to interpretation because relatively few pathologic specimens are often the foundation for selected terminology. Noninvasive diagnostic tests including lung function testing and imaging are frequently nonspecific, particularly for the small airways. Further, when deciding whether to recommend surgical or thoracoscopic lung biopsy, health care providers are charged with performing risk-benefit analyses in which potential surgical and anesthetic risks might not justify anticipated results. Moreover, occupational bronchiolitis is relatively rare and workplace exposures might not be considered early during the diagnostic evaluation, which can result in the misdiagnoses of more common airways diseases, such as asthma or chronic obstructive pulmonary disease (COPD).[5]

In this report, we provide an update on some known causes of occupational bronchiolitis based on the published literature from 2009 to 2018. We cover flavoring-related lung disease caused by exposure to diacetyl and 2,3-pentanedione, constrictive bronchiolitis associated with military deployment, and emerging issues such as occupational bronchiolitis associated with the fiberglass-reinforced plastic industry and industrial machine manufacturing. For these

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occupational exposures that can potentially result in small airways disease, our knowledge continues to expand as additional studies are published. Much of the literature to date consists of case reports, case series, and other observational epidemiologic studies, but research methods are beginning to include more systematic or standardized approaches to describe and understand these diseases. Inevitably, we will learn of novel occupational exposures that can cause small airways diseases in the future, and we will continue to rely on astute health care providers to suspect workplace exposures and public health agencies to conduct follow-up investigations.

FLAVORINGS

Flavoring-related lung disease (FRLD) was first described in 2002 among former workers at a sentinel microwave popcorn production facility.[6,7] Clinical progression was insidious and marked by exertional dyspnea and cough. The patients had fixed obstruction on spirometry testing, and lung pathology findings for those who underwent biopsy were consistent with bronchiolitis obliterans based on inflammation and fibrotic changes leading to narrowing of the bronchioles.[6,7] Diacetyl (2,3-butanedione), a butter flavoring chemical, was the predominant compound detected on air sampling, and a strong relationship between cumulative diacetyl exposure and airways obstruction was observed among current workers.[6] Experimental animal studies subsequently revealed inhalation exposure to diacetyl caused severe injury to the respiratory epithelium, implicating diacetyl as the cause of FRLD.[8–11] Alpha-diketones structurally similar to diacetyl that differ in the number of carbon groups, including 2,3-pentanedione, 2,3-hexanedione, and most recently methylglyoxol, have demonstrated similar toxicity in animal studies.[12–15] Additional epidemiologic investigations supported the association between occupational exposure to diacetyl and bronchiolitis in microwave popcorn production and flavoring manufacturing.[16–18]

Findings from select case reports, case studies, and epidemiologic studies related to FRLD from 2009 to 2018 are summarized in **Table 1**. Since the initial investigation of the sentinel microwave popcorn facility, additional cases of FRLD have been diagnosed among workers in other microwave popcorn facilities and other industries, including flavoring manufacturing, snack food production, pet food production, and coffee roasting and packaging facilities.[16,19–24] Most FRLD cases have been associated with occupational exposure, although in 2012 Egilman and Schilling[25] reported 3 cases of FRLD that they attributed to microwave popcorn consumption.

Understanding of the clinical characteristics has improved since the identification and description of the sentinel cluster. The most commonly reported symptoms are exertional dyspnea and dry cough; however, chest tightness and upper respiratory symptoms also can occur.[6,26,27] Fixed obstruction on spirometry is the most common pattern on lung function testing, although 28% (30 of 106) of flavoring manufacturing workers in one study had restrictive patterns on spirometry.[20,21,28–30] Mixed and normal spirometry patterns also have occurred.[5,25] High-resolution computed tomography (HRCT) commonly demonstrates mosaic attenuation consistent with air trapping, but results are not specific to FRLD.[20,28] The diagnosis of most FRLD cases is based on work and exposure history, signs and symptoms, and noninvasive diagnostic testing results.

Lung biopsy of workers with FRLD can lead to false negative results because of patchy distribution of bronchiolar inflammation.[31,32] Compared with transbronchial biopsy, surgical biopsy is the more sensitive method if pursuing a pathologic diagnosis. Several workers from the sentinel microwave popcorn plant who underwent lung biopsy and histopathology demonstrated narrowing and fibrosis of the bronchioles that led to the pathologic diagnosis of bronchiolitis obliterans.[7] However, as additional cases of FRLD have been diagnosed, the observed histopathology results have varied and included granulomatous inflammation, pleural proliferation of mesothelial cells or eosinophils, emphysema, and interstitial fibrosis.[17,20,21,33] A study analyzing a series of pathologic specimens from flavoring-exposed workers would be a useful contribution to our understanding of the potential disease spectrum.

FRLD is often misdiagnosed because more common obstructive lung diseases, including asthma or COPD, are typically considered.[5] The misdiagnoses are likely attributable to the relatively rare occurrence of FRLD, the absence of a thorough occupational exposure history, and the attribution of the condition to cigarette smoking.[34] Consequently, FRLD should be considered as a possible diagnosis in any worker who presents with breathing difficulty and is exposed at work to diacetyl or other flavoring-related compounds. There is no specific treatment for FRLD other than removing the individual from the exposure and supportive treatment.[35] There have been mixed results following treatment with steroids or other anti-inflammatory agents.[36] Lung transplantation is an option for end-stage disease, although lung function might stabilize after cessation of exposure.[37]

Table 1
Flavoring-related lung disease case reports, case series, or epidemiologic studies, 2009–2019

Authors	No. Cases (% Male)	Diagnosis/ Terminology	Symptoms	Pulmonary Function Testing	HRCT	Histology	Exposures/ Tobacco Exposures	No. Workers/ Other
Lockey et al.[38] 2019	–	–	–	Workers with historically higher exposure from first cohort (mixers) had a significant decline in % FEV1 during 7-y study period; study participants had increased restrictive lung patterns compared with general US population	–	–	3 exposure cohorts that represented dates of diacetyl substitution and introduction of engineering and administrative controls, and respiratory protection to reduce exposure	1105 workers evaluated; 7-y study at 4 microwave popcorn facilities with 3 cohorts

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Table 1
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Authors	No. Cases (% Male)	Diagnosis/ Terminology	Symptoms	Pulmonary Function Testing	HRCT	Histology	Exposures/ Tobacco Exposures	No. Workers/ Other
Fechter-Leggett et al.[4] 2018	4 (pathologist-reported) (75%); 48 (probable) (50%)	Constrictive bronchiolitis or bronchiolitis obliterans	3 of 4 exertional dyspnea; 4 of 4 usual cough (pathology-reported); 92% exertional dyspnea, 65% usual cough (probable)	2 (50%) obstruction, 2 (50%) mixed (pathology reported); 21% obstruction; 79% mixed (probable)	—	Constrictive bronchiolitis or bronchiolitis obliterans (also granulomas, respiratory bronchiolitis, and emphysema in 4 pathology-reported cases)	Microwave popcorn or flavoring manufacturing facilities;3 of 4 never smoker (pathology-reported)35% never smoker (probable)	1407 workers evaluated from 8 microwave popcorn or flavoring manufacturing facilities; 7 of 11 workers with biopsy did not meet pathology-reported case definition (granulomas, respiratory bronchiolitis, chronic fibrous pleuritis, interstitial fibrosis, peribronchial inflammation, emphysema)
Harvey et al.[40] 2018	1 (100%)	Flavoring-related lung disease	Chest tightness, mucous membrane irritation, dyspnea, cough	Moderate mixed pattern	Mosaic attenuation consistent with diffuse bilateral air trapping	Focal mild cellular bronchiolitis and pleuritic, and focal peribronchial giant cells/ granulomas	Flavoring coffee: 521–2173 ppb diacetyl and 345–1445 ppb 2,3-PD; TWA 41–421 ppb diacetyl and 22–276 ppb 2,3-PD	

Warrior et al.[41] 2018	1 (100%)	Flavoring-induced bronchiolitis obliterans syndrome	Chronic cough	Severe obstruction with air trapping and mild gas transfer defect	Biapical scarring and bilateral bronchiectasis	—	Flavoring pet food	
Morales-Camino [24] 2016	–	—	—	5.6% of workers with excessive decline in FEV1 or FVC	—	—	—	479 workers evaluated at potato chips factory
Bailey et al.[39] 2015	5 former workers (NR)	Obliterative bronchiolitis	More dyspnea compared with general population	More obstruction compared with general population	—	2 former workers with biopsy-confirmed obliterative bronchiolitis	Maximum TWA 283 ppb combined diacetyl and 2,3-PD; maximum STEL 14,300 ppb diacetyl and 18,400 ppb 2,3-PD	75 current workers and 13 formers workers evaluated at coffee facility
Kreiss[29] 2014	–	—	—	More spirometric restrictive pattern than expected; excessive decline in FEV1 in 19% of workers	—	—	Maximum TWA 10.17 ppm diacetyl	106 flavoring manufacturing workers evaluated

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Authors	No. Cases (% Male)	Diagnosis/ Terminology	Symptoms	Pulmonary Function Testing	HRCT	Histology	Exposures/ Tobacco Exposures	No. Workers/ Other
Cummings et al.[27] 2014	–	Subclinical obliterative bronchiolitis	Dyspnea associated with tenure ≥7 y, other chest symptoms associated with time in production	Mean spirometric parameters lower in workers with tenure ≥7 y or ≥1 h daily in production; mean diffusing capacity lower in workers with tenure ≥7 y	—	—	Flavoring manufacturing	367 current workers evaluated at flavoring manufacturer
CDC [20] 2013	2 (50%)	Obliterative bronchiolitis	Cough, exertional dyspnea	Obstruction	Bronchial wall thickening, prominent mosaic pattern, mild cylindrical bronchiectasis, fibrotic scarring	Constrictive bronchiolitis with narrowed and obliterated airways with surrounding fibrous tissue and variable mixed chronic inflammatory cell infiltrate; chronic and subacute small airways injury	Mixers in the flavoring room of a coffee processing facility	Both misdiagnosed before obliterative bronchiolitis diagnoses

Halldin et al.[5] 2013	4 (NR)	"Other COPD"-associated deaths	3 usual cough, 2 shortness of breath	1 obstruction, 2 mixed patterns	—	—	Microwave popcorn; diacetyl 1.99 ppm average exposure (range: 0.004–9.74 ppm); 2 never smokers	Respiratory-associated mortality study of 15 deaths identified among 511 workers at sentinel microwave popcorn facility; no ICD code for bronchiolitis obliterans
Huff et al.[23] 2013	5 (NR)	Bronchiolitis obliterans	Cough, wheeze, exertional dyspnea	Severe fixed obstruction	Upper lobe reticular nodular abnormalities with bronchial wall thickening, mild cylindrical bronchiectasis	2 of 5 with biopsy; chronic and subacute small airways injury suggestive of proliferative and obliterative constrictive bronchiolitis	Coffee flavoring	
Kreiss et al.[30] 2012	–	—	—	Excessive decline in lung function associated with companies using more diacetyl during production	—	—	Flavoring manufacturing	Evaluation of spirometry data from 724 flavoring manufacturing workers in California

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Authors	No. Cases (% Male)	Diagnosis/ Terminology	Symptoms	Pulmonary Function Testing	HRCT	Histology	Exposures/ Tobacco Exposures	No. Workers/ Other
Cavalcanti et al.[21] 2012	4 (100%)	Bronchiolitis obliterans	Cough, shortness of breath, wheeze	Moderate to severe obstruction	Hyperinflation, air trapping, bronchial thickening, mosaic perfusion	1 of 4 with biopsy; slight distortion of small airways with airway wall smooth muscle hypertrophy, mild mononuclear cell infiltrate, and area of air trapping and hyperinflation; single non-necrotic epithelioid granulation with multinucleated giant cells in subpleural space	Brazilian cookie factory with artificial butter flavoring	
Egilman and Schilling [25] 2012	3 (33%)	Bronchiolitis obliterans	Exertional dyspnea, cough, wheeze	1 normal spirometry; 1 decreased FEV1; 1 restriction pattern	1 ground glass opacity; 1 bibasilar atelectasis and lingular infiltrate; 1 mosaic pattern	Mild constrictive bronchiolitis with granulomas	Butter flavored microwave popcorn consumers	Nonoccupational exposure

Kanwal et al.[41] 2011	–	—	Workers with past high exposure had stable respiratory symptoms and new workers had fewer respiratory symptoms	New workers had higher lung function than worker with past high exposures	—	—	Engineering controls reduced diacetyl exposures by 1 to 3 orders of magnitude	373 current workers evaluated in follow-up study from sentinel microwave popcorn facility
Kim et al.[28] 2010	8 (NR)	Bronchiolitis obliterans or fixed obstructive related to flavorings	Dyspnea, cough, wheeze most common	Moderate to severe fixed obstruction	4 of 7 with HRCT consistent with bronchiolitis obliterans	2 biopsies: 1 consistent with bronchiolitis obliterans, 1 interpreted as hypersensitivity pneumonitis	Flavor manufacturing workers in California	467 workers evaluated from 16 flavoring manufacturing facilities using medical surveillance data
Van Rooy et al.[22] 2009	4 (NR)	Bronchiolitis obliterans syndrome	Trouble breathing, cough, wheeze, asthma attack	Excessive decline in FEV1 (cohort)	—	—	Dutch food flavoring production; 1.8–351 mg/m^3 historic exposure, 3–396 mg/m^3 for specific tasks	175 workers evaluated from plant producing diacetyl in historic cohort study

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Table 1 (*continued*)

Authors	No. Cases (% Male)	Diagnosis/ Terminology	Symptoms	Pulmonary Function Testing	HRCT	Histology	Exposures/ Tobacco Exposures	No. Workers/ Other
Lockey et al.[18] 2009	–	Bronchiolitis obliterans	—	Lower % predicted FEV1 and 8-fold increased risk of airway obstruction associated with diacetyl exposure	—	—	High cumulative diacetyl exposure (≥8 ppm-y) prior to respiratory use associated with lower % predicted FEV1 and eight-fold increased risk of airway obstruction	765 workers evaluated from 4 microwave popcorn production plants

Abbreviations: '—', not performed/evaluated; 2, 3-PD, 2, 3-Petanedione; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; NR, not reported; PFT, pulmonary function tests; ppb, parts per billion; ppm, parts per million; STEL, short term exposure; TWA, time-weighted average.

The risk of FRLD is established among microwave popcorn production workers. In response, strategies to reduce diacetyl exposure in the industry have included substitution, engineering controls, administrative controls, and respiratory protection. A recent study evaluated change in lung function over time in more than 1000 microwave popcorn workers and demonstrated the historically high-exposure group had a significant decrease in percent predicted FEV_1 during the 7-year study period.[38] Although the risk of FRLD has been recognized in microwave popcorn production for nearly 2 decades, FRLD cases continue to be identified in new industry settings in which flavorings are added during production.[39–41] Management in industrial settings where flavorings are used but where cases have not been identified might not be aware of the risk for occupational lung disease. In addition, the hazards might not be communicated appropriately in Safety Data Sheets of flavoring formulations, including those for diacetyl and 2,3-pentanedione.[42]

FRLD is preventable. Engineering controls such as enclosing the flavoring room in industries that use flavorings during production, or adding local exhaust ventilation can substantially reduce exposures.[43] These controls have also proven effective in stabilizing workers' lung function in some settings.[44] Personal protective equipment (PPE), such as a half mask respirator with organic vapor cartridge is required in some settings, although PPE should not be relied on as the primary source of protection. Substituting other alpha-diketones such as 2,3-petanedione or 2,3-hexanedione for diacetyl is not considered a safe alternative based on animal studies demonstrating similar pathologic findings following exposure. The National Institute for Occupational Safety and Health (NIOSH) recommends medical surveillance, including respiratory symptom screening and spirometry every 6 months for workers who regularly work in or enter areas where alpha-diketones are used.[45] Early detection of abnormal spirometry or excessive decline in lung function over time and subsequent removal from further exposure to diacetyl or other alpha-diketones is important to prevent the progression of FRLD.[28] In 2006, the California Department of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA), and California Department of Public Health initiated an industrywide surveillance program for flavoring manufacturing that included diacetyl exposure assessments, engineering controls, spirometry for workers, and PPE requirements.[28,30]

The US Department of Labor's Occupational Safety and Health Administration (OSHA) has no permissible exposure limits for alpha-diketones. NIOSH published recommended exposure limits of 5.0 parts per billion (ppb) for diacetyl and 9.3 ppb for 2,3-pentanedione for time-weighted averages (TWAs) for a 40-hour workweek in 2016. The NIOSH short-term exposure limits (STELs) are 25 ppb for diacetyl and 31 ppb for 2,3-pentanedione.[46] The American Conference of Governmental Industrial Hygienists published a threshold limit value (TLV) TWA of 10 ppb and an STEL of 20 ppb for diacetyl, and has placed 2,3-pentanedione on the 2017 list of Chemical Substances and Other Issues under study.[47,48]

Diacetyl has been detected during processes and tasks in industries not associated with FRLD. For instance, diacetyl is naturally produced during some production processes including coffee roasting and marijuana processing, although we are not aware of FRLD cases attributed to natural sources of diacetyl.[49–51] E-cigarette and vaping products commonly contain diacetyl and other flavorings[52]; case reports in e-cigarette and vaping product consumers include severe lung disease that is the subject of ongoing inquiry.[53–55]

SOUTHWESTERN ASIA DEPLOYMENT

Cases of constrictive bronchiolitis have been attributed to inhalation exposures that occurred during military deployments to Iraq and Afghanistan as part of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).[56–60] Military personnel who served in Southwestern Asia as part of OIF/OEF often experienced inhalation exposures to sandstorms, dust, diesel exhaust, open air burn pits, and cigarette smoke, and some experienced combat-related exposures, including weapons firing and exposures to blasts from improvised explosive devices.[61–64] These inhalation exposures prompted concerns for the development of long-term respiratory symptoms related to deployments during OIF/OEF and led to the Department of Veterans Affairs establishing the Airborne Hazards and Open Burn Pit registry to identify health effects associated with inhalation exposures during Southwestern Asia military deployments.[65] As of July 31, 2015, of 42,558 registry respondents who had deployed to Southwestern Asia since October 7, 2001, 433 (1%) self-reported a health care provider diagnosis of constrictive bronchiolitis; these respondents more often reported burn pit exposure compared with those without a diagnosis of constrictive bronchiolitis.[66]

From 2004 to 2009, King and colleagues[57] evaluated 80 soldiers from a single US Army base who were referred for evaluation of respiratory symptoms and exercise intolerance following deployments during OIF/OEF. Thirty-eight of the 49 soldiers who underwent video-assisted thoracoscopic lung biopsies were determined to have constrictive bronchiolitis following nonblinded specimen review by 2 pathologists (**Table 2**). More than 80% were never smokers or former smokers. Twenty-eight were exposed to a sulfur-mine fire near Mosul in 2003. Occupational histories varied and included exposure to burn pits, incinerated human waste, dust storms, and combat smoke. More than 33% had normal spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide (DLCO). One-half had normal spirometry and isolated low DLCO. Only 4 had abnormal spirometry, including 3 with a restrictive pattern and 1 with an obstructive pattern. Among the 37 soldiers who underwent HRCT, 25 (68%) had normal HRCTs and 6 (16%) had mild air trapping. Lacy black pigment was noted in the visceral pleural surface following lung biopsy for 37 of the 38 soldiers. Prominent pathologic features included pigment deposition (n = 37), polarizable material within pigment (36), peribronchiolar inflammation (34), hypertensive-type arterial change (28), and prominent bronchial-associated lymphoid tissue (19). Luminal constriction was observed in 64% of sampled terminal and respiratory bronchioles. The alveolar structures and larger airways were typically normal. This case series demonstrated the possibility for inhalation exposures that occurred during military deployments to Iraq to be the source of constrictive bronchiolitis, a rare lung disease, among this previously healthy cohort.

Since publication of the series of King and colleagues[57] in 2011, 50 other cases of bronchiolitis associated with military deployments during OIF/OEF have been described (see **Table 2**).[56,58,60,67–69] Forty-one of these patients were described as having bronchiolitis, 6 constrictive bronchiolitis, 2 respiratory bronchiolitis, and 1 as nonspecific interstitial pneumonitis and bronchiolitis. Krefft and colleagues[68] used a case definition to identify 87 cases of distal deployment-related lung disease (DDLD) among 127 military or civilian workers who presented consecutively to a specialty clinic with new-onset respiratory symptoms that began during or following military-related deployments. Thirty-one (60%) of 52 of these patients who underwent lung biopsies were identified as having bronchiolitis; each of the 52 patients who underwent lung biopsy had at least 1 histologic abnormality. No additional data were provided by Krefft and colleagues[68] specifically for the 31 biopsy-confirmed cases of bronchiolitis or by Madar and colleagues[69] for the 2 cases of respiratory bronchiolitis. For the remaining 17 patients from the 7 other studies that reported additional data, 16 (94%) patients presented with exertional dyspnea.[56,58–60] Seven of these patients had additional clinical information, of whom 2 had normal spirometry. Only 1 of the 6 patients who had HRCT findings reported a normal HRCT compared with 68% of the patients described by King and colleagues.[56–60] Each of the 5 patients who had an available smoking history was a never smoker.[56,58,60] Deployment histories included Iraq (n = 4), Afghanistan (n = 2), Middle East (n = 1), and not reported (n = 2). Since the identification of cases of constrictive bronchiolitis associated with OIF/OEF, 2 cases of constrictive bronchiolitis among veterans of Gulf War I also have been described (see **Table 2**).[70,71]

Following a systematic review, Banks and colleagues[72] analyzed 41 cases of military deployment–related constrictive bronchiolitis compared with a cohort of cases of constrictive bronchiolitis related to other causes including occupational exposure to artificial flavorings and exposure to sulfur mustard gas. Compared with constrictive bronchiolitis from other causes, the cohort of military deployment–related cases had the following statistically significant differences ($P<.05$) in prevalences of clinical findings: (1) lower prevalences of spirometric obstruction, abnormal chest radiography, and CT/HRCT not consistent with constrictive bronchiolitis; and (2) higher prevalences of abnormal diffusing capacity.[72] A small case series demonstrated that of 6 patients with deployment-related biopsy-proven bronchiolitis, each had abnormalities on noncontrast chest CT, including centrilobular nodularity (n = 6), bronchial wall thickening (2), air trapping (2), and ground glass opacities (1).[67] Further, investigators used field-emission scanning electron microscopy and laser ablation inductively coupled plasma mass spectrometry to analyze lung tissue specimens from 11 military personnel who had deployed to Southwestern Asia and undergone subsequent lung biopsy because of respiratory symptoms, several of whom were confirmed to have had constrictive bronchiolitis.[73,74] Compared with negative controls (n = 11) and positive controls (n = 11) who had autoimmune constrictive bronchiolitis, the lung tissue specimens from the symptomatic military personnel had higher abundances of silicon, cadmium, aluminum, and vanadium.[73] The findings from this small case series exhibit the possibility that these metals could play a role in the development of constrictive bronchiolitis related to military deployment.

Table 2
Southwestern Asia military deployment-related bronchiolitis cases

Authors	No. Cases (% Male)	Diagnosis	Symptoms	PFTs	HRCT	Histology	Deployment Exposures/ Tobacco Exposures	Other
Gulf War I								
Robinson and Barney [70] 2018	1 (100%)	Constrictive bronchiolitis	Progressive exertional dyspnea; episodic coughing and wheezing	Restriction; FVC = 45% predicted; TLC = 57% predicted; DLCO = 64% predicted Required 4 L oxygen on 6MWT to maintain normal oxygen saturation	Bilateral lower lobe atelectasis and bilateral air trapping on expiratory views	Constrictive bronchiolitis; airway-centered antraco-silicotic dust; SEM/EDX = aluminum and magnesium silicates; titanium dioxide; rare earth elements (cerium and lanthanum); antimony; chromium	Veteran of Gulf War (Saudi Arabia, Kuwait, Iraq during 1990–1991) Sandstorms, Kuwait oil fires Nonsmoker	

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Table 2 (*continued*)

Authors	No. Cases (% Male)	Diagnosis	Symptoms	PFTs	HRCT	Histology	Deployment Exposures/ Tobacco Exposures	Other
Weiler et al.[71] 2018	1 (100%)	Constrictive bronchiolitis	Progressive exertional dyspnea	1992 — FEV1 = 5.41 L (123% predicted); FVC = 7.36 L (132%); FEV1/FVC = 0.73 1994 — FEV1 = 4.75 L (109%); FVC = 6.51 L (118%); FEV1/ FVC = 0.73 2016 — FEV1 = 2.83 L (78%); FVC = 4.32 L (88%); FEV1/FVC = 0.65; TLC = 6.96 L (92%); RV = 2.26 L (86%); DLCO = 20.3 mL/min/mm Hg (70%)	Inspiratory = mild bibasilar atelectasis and old granul- omatous disease Expiratory = diffuse air trapping	Small airways abnormalities (muscular hypertrophy, luminal narrowing, diminution of size compared with paired pulmonary artery) Middle lobe had focal organizing pneumonia and a few isolated granulomas No evidence of foreign material in sample No birefringent particulates	Two Persian Gulf deployments during 1991 and 1992 (burning oil wells; petrochemical cracking facilities; burned tanks that had been hit by depleted uranium penetrating rounds; downwind several hundred miles from plume from detonation of Khamisiyah Ammunition Storage Facility; dust storms; pesticide impregnated uniforms; weapons firing; CS tear gas) Never smoker	

Operation Iraqi Freedom/Operation Enduring Freedom							
King et al.[57] 2011	38 (92%)	Constrictive bronchiolitis	Exertional dyspnea	Normal = 13 (34%) Normal with low DLCO = 19 (50%) Obstructive = 2 (5%) Restrictive = 3 (8%) Mixed obstructive/ restrictive = 1 (3%)	Normal = 25 (68%)[a] Mild air trapping = 6 (16%) >1 nodules (<1 cm) = 2 (5%) Solitary nodule (<1 cm) = 1 (3%) Pleural thickening = 1 (3%) Bibasilar scarring = 1 (3%) Apical bullae = 1 (3%)	Bronchiolar luminal constriction = 38 (100%) Predominant c onstrictive stroma = 38 (100%; smooth muscle [7], fibrous tissue [3], mixed [28]) Pigment deposition = 37 (97%) Polarizable material within pigment = 36 (95%) Peribronchiolar inflammation = 34 (89%) Hypertensive-type arterial change = 28 (74%) Respiratory bronchiolitis = 27 (71%) Prominent bronchial-associated lymphoid tissue = 19 (50%) Mucus plugging = 13 (34%) Eosinophils in bronchiolar wall = 7 (18%) Luminal granulation = 2 (5%)	Dust storms = 33 (87%) Sulfur-mine fire in 2003 = 28 (74%) Incinerated solid waste = 24 (63%) Incinerated human waste = 18 (47%) Combat smoke = 17 (45%) Current smoker = 7 (18%) Former smoker = 6 (16%)

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Table 2
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Authors	No. Cases (% Male)	Diagnosis	Symptoms	PFTs	HRCT	Histology	Deployment Exposures/ Tobacco Exposures	Other
						Obliteration of bronchioles = 0 (0%)		
Szema et al. [79] 2012	1 (100%)	Nonspecific interstitial pneumonitis and bronchiolitis	Cough, wheeze	NR	NR	Nonspecific interstitial pneumonitis with peribronchiolar inflammation; lung section had evidence of iron, copper, titanium	Deployed to Iraq and Kuwait; airborne dust in laundry facility; improvised explosive device; sandstorms; burn pits; occasional cigar	
Dhoma et al.[67] 2014	10 (NR)	Bronchiolitis	Exertional dyspnea	NR	NR	NR	NR	
Osman et al.[59] 2014	1 (100%)	Constrictive bronchiolitis	Progressive dyspnea on exertion	No obstruction; TLC = 74% predicted	Focal bronch-iectasis within right lower and middle lobes	Constrictive bronchiolitis	Deployed to Iraq in 2008; burn pits	Evaluated 6 y after deployment

Lentz et al.[58] 2016	3 (100%)	Constrictive bronchiolitis	Exertional dyspnea	Patient 1 PFT pattern = normal; FEV1 (% predicted) = 94%; FVC = 89%; TLC = 100%; DLCO = 108% Patient 2 PFT pattern = normal; FEV1 (% predicted) = 81%; FVC = 78%; TLC = 80%; DLCO = 92% Patient 3 PFT pattern = mixed obstruction/ restriction; FEV1 (% predicted) = 66%; FVC = 78%; TLC = 64%; DLCO = 97%	Patient 1 3 mm nodule Patient 2 Right middle lobe bronchial thickening Patient 3 Mild air trapping	Cryobiopsy diagnostic of constrictive bronchiolitis (n = 3) Peribronchial pigment deposition (n = 3)	Patient 1 Iraq Burn pits Combat smoke Never smoker Patient 2 Afghanistan Burn pits Never smoker Patient 3 Iraq Afghanistan Burn pits Never smoker	Diagnosis made following cryobiopsy
Madar et al.[69] 2017	2 (NR)	Respiratory bronchiolitis	NR	NR	NR	NR	NR	2 cases occurred among 137 deployed military personnel with lung biopsies (1%) compared with 4 cases among 254 non-deployed personnel (2%), p = NS
Papieniak et al.[60] 2018	1 (100%)	Constrictive bronchiolitis	Progressive exertional dyspnea	Pulmonary function testing lower limits of normal for age 6MWT reduced at 298 m; required 3 L oxygen with exertion	Normal	Constrictive bronchiolitis	Middle East deployment, multiple exposures, burn pits Never smoker	Former triathlete; 6MWT increased to 426m after beginning thrice weekly azithromycin

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(*continued*)

Authors	No. Cases (% Male)	Diagnosis	Symptoms	PFTs	HRCT	Histology	Deployment Exposures/ Tobacco Exposures	Other
Butzko et al.[56] 2019	1 (0%)	Constrictive bronchiolitis	Progressive dyspnea	Pre-BD spirometry (% predicted)[b] FEV1 = 2.35 L (81%); FVC = 2.86 L (81%); FEV1/FVC = 0.82; TLC = 3.68 L (80%); RV = 0.71 L (50%); DLCO = 19.10 mL/min/mm Hg (84%) Pre-BD FOT (%predicted) Rrs 4 = 8.06 hPa/L/s (148%); Rrs 4-Rrs 20 = 2.56; Xrs 4 = −2.42 (117%); Ax4 = 40.79 Hz• hPa/L/s (342%); Fres = 31.56 (183%) Post-BD FOT (% change)< Rrs 4 = 2.88 hPa/L/s (−64%); Rrs 4-Rrs 20 = −1.18 (−146%); Xrs 4 = −0.81 (−71%); Ax4 = 5.68 Hz•hPa/L/s (−86%); Fres = 5.68 (−51%)	Widespread large and small airway thickening, mild distortion most prominent in lung bases, subtle mosaic attenuation	Constrictive bronchiolitis with secondary airspace enlargement	12-mo deployment to Iraq in 2005; burn pits; dust; sand storms Never smoker	Respiratory symptoms began within 2 mo of arriving in Iraq and episode of pneumonia; frequent bronchitis and dyspnea on exertion; symptoms persisted post-deployment and refractory to therapy; diagnosis made 9.5 y post-deployment;

Krefft et al.[68] 2020	31 (NR)	Bronchiolitis	Cough, shortness of breath, chest tightness/ wheezing	Normal = 52/80 (65%); obstruction = 4/80 (5%); restriction = 20/80 (25%); air trapping (RV>120% predicted) = 36/77 (47%); abnormal DLCO = 18/77 (23%); any abnormality = 55/80 (69%)	34/118 (29%) met case definition for probable DDLD[c]	31/52 (60%) patients who underwent lung biopsies had bronchiolitis		For all DDLD cases: Iraq, Afghanistan, Iraq/Afghanistan, other conflict areas; mean deployment duration = 20.3 mo; mean number of deployments = 2.1 For all DDLD cases: Never smoker = 53%; ex-smoker = 43%; current smoker = 3%	All 52 patients who underwent lung biopsy had at least one histologic abnormality; hyperinflation/ emphysema = 69%; granulomatous pneumonitis accompanied by lymphocytic interstitial inflammation = 50% 18/77 (23%) of DDLD patients had abnormal DLCO compared with 0/20 (0%) with proximal respiratory disease, $P = .02$

Abbreviations: 6MWT, 6 minute walk test; Ax4, reactance curve area calculated either between 4 hertz and resonant frequency; BD, bronchodilator; cm, centimeter; DDLD, deployment-related distal lung disease; DLCO, diffusing capacity of the lungs for carbon monoxide; EDX, energy dispersive X-ray spectroscopy; FEV1, forced expiratory volume in 1 second; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; hPa, hectopascal; HRCT, high-resolution computed tomography; Hz, hertz; L, liter; min, minute; ml, milliliter; mm, millimeter; NR, not reported; NS, not significant; PFT, pulmonary function tests; Rrs, resistance; RV, residual volume; s, second; SEM, scanning electron microscopy; TLC, total lung capacity; Xrs, reactance.

[a] 37 of 38 soldiers underwent high-resolution computed tomography testing.

[b] No significant change post-bronchodilator.

[c] Deployment-related distal lung disease defined as military or civilian patients who had respiratory symptoms (ie, cough, shortness of breath, or chest tightness/wheezing) that began during or after deployment and (a) Definite = 1 or more of the following surgical lung biopsy findings: hyperinflation or emphysema; bronchiolitis, small airways inflammation, peribronchiolar fibrosis; or granulomatous pneumonitis, or (b) Probable = 2 or more of the following chest computed tomography findings: centrilobular nodularity, air trapping or mosaicism, or bronchial wall thickening.

Despite concerns over the potential for inhalation exposures experienced during OIF/OEF to be the source of constrictive bronchiolitis and other respiratory diseases, conclusive evidence remains elusive.[61,64,75] The Millennium Cohort study that evaluated deployment and burn pit exposure during 2004 to 2008 determined that no increased likelihood existed for newly reported asthma, newly reported chronic bronchitis or emphysema, or self-reported respiratory symptoms among military personnel exposed to burn pits compared with other deployed military personnel.[64] In addition, the Institute of Medicine's Committee on the Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan was unable to render a conclusion whether long-term health effects are caused by exposure to the burn pit at Joint Base Balad in Iraq, but did note that long-term health effects might result from air pollution in Iraq and Afghanistan that originates from sources other than burn pits.[61] More recently, investigators evaluated a cohort of 50 military personnel who had developed respiratory symptoms within 6 months of returning from deployment in 2010.[76] Initial health assessments failed to yield a clinical diagnosis for 21 patients. A total of 37 patients had normal HRCTs, but unlike the case series described by King and colleagues,[57] none of the patients underwent lung biopsy.[76]

The likelihood of identifying a specific causal agent as the source of deployment-related bronchiolitis is low considering that (1) to date, fewer than 50 of the more than 2.7 million service members deployed to OIF/OEF have been described in the published literature as having deployment-related bronchiolitis[56–60,67,69,77]; (2) establishing a standardized case definition for the histologic diagnosis of constrictive bronchiolitis has proven challenging[78]; (3) some patients were deployed multiple times to different locations[58,79]; (4) patients had multiple, varying, and not well-characterized exposures[56–60,67,69,79,80]; and (5) the challenge in characterizing the timing of specific known exposures with respect to disease onset.[81] Additional well-designed epidemiologic studies are needed to further describe the association between military deployments to Southwestern Asia and constrictive bronchiolitis with particular attention given to possible individual host susceptibility factors.

EMERGING ISSUES

Multiple reports in recent years have drawn attention to novel or previously unrecognized risk factors for occupational bronchiolitis. A case series published in 2013 described 6 cases of obliterative bronchiolitis in fiberglass-reinforced plastics workers: 5 boat builders and 1 water cooling tower fabricator from 5 different worksites.[82] The cases were remarkable for their severity with outcomes that included 2 lung transplants and 1 death. The industrial process associated with each case involved fabrication of fiberglass-reinforced plastics using a resin mixed with styrene and an accelerating agent. High concentrations of styrene and dimethyl phthalate were found in the workplace air of 1 patient, and for other cases chemical exposures were thought to include acetone, butyl acetate, butanone, N,N-diethylaniline, diethylene glycol, and isophorone diisocyanate. This series prompted the reporting of 2 additional cases in a yacht builder and water storage tank repairer, who shared exposures to chemicals used in lamination, including polyester resin, methyl ethyl ketone peroxide, and styrene.[83]

Epidemiologic studies of the fiberglass-reinforced plastics industry also indicate respiratory disease consistent with bronchiolitis. One clue originated from cancer mortality studies demonstrating unanticipated excess mortality from nonmalignant respiratory diseases such as COPD.[84] In particular, the occurrence of COPD deaths among short-tenure workers who had high styrene exposures raises the possibility of misdiagnosed bronchiolitis among workers who left employment early in their tenure after being disabled by occupational exposure.[85] In one example, longitudinal analysis of a cohort of 5204 workers from 2 fiberglass-reinforced plastic boatbuilding facilities found short-tenure, high-exposure workers had elevated standardized mortality ratios for nonmalignant respiratory disease (1.99; 95% confidence interval [CI] 1.38–2.79) and COPD (2.60; 95% CI, 1.70–3.81).[86] When we examined death certificates and available medical records for decedents from this cohort who died of nonmalignant respiratory disease, we found 1 case of bronchiolitis and 9 cases of early-onset COPD that could represent misdiagnosed bronchiolitis.[87] Planned follow-up of this cohort to characterize the respiratory health of survivors might further elucidate the risk of bronchiolitis among workers in this industry.

The fiberglass-reinforced plastics industry is notable for its chemical complexity and determining the exposure(s) responsible for occupational bronchiolitis among these workers is challenging. At a manufacturing facility that made fiberglass-reinforced windblades for the green energy sector, styrene was the predominant exposure, with high peak concentrations associated with certain tasks.[88] Evaluation of the workforce demonstrated associations between chest symptoms, spirometric obstruction, other functional deficits, and estimated styrene exposure using urinary metabolites.[89] Styrene is a readily absorbed volatile organic compound (VOC) and a plausible respiratory toxin given its observed effects on respiratory epithelium in some animal models.[84] Nevertheless, the toxicologic literature on styrene is not uniform,[90,91] and it is possible that associations between adverse respiratory outcomes and

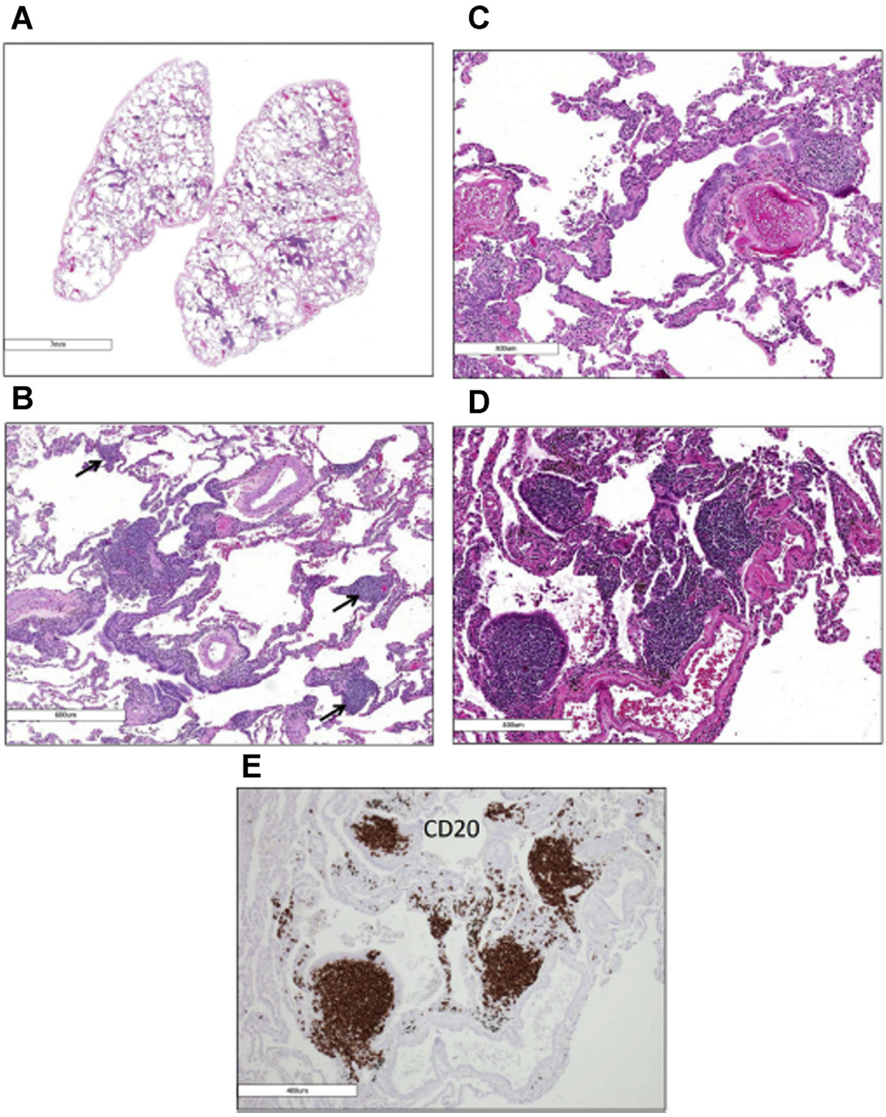

Fig. 1. Representative hematoxylin and eosin stains of explanted lung tissue and surgical lung biopsies from patients with lymphocytic bronchiolitis, alveolar ductitis, and emphysema (BADE). These specimens highlight the primary histologic features of lymphoplasmacytic infiltrates with primary lymphoid follicles around the distal airways and notable involvement of respiratory bronchioles and alveolar ducts, in addition to diffuse emphysema. (*A*) Low-power view, highlighting peribronchiolar lymphoid aggregates with widespread emphysema. (*B*) Medium-power view, showing nonreactive lymphoid follicles with nodular extensions into the alveolar ducts (*arrows*); emphysema also appreciated. (*C, D*) High-power views of nodular lymphoid aggregates around a respiratory bronchiole and chronic inflammatory infiltrates expanding the walls of the alveolar ducts. (*E*) Immunochemical staining for CD20, a B-cell marker, demonstrating B cells make up most of the primary follicles. (*From* Cummings KJ, Stanton ML, Nett RJ, et al. Severe lung disease characterized by lymphocytic bronchiolitis, alveolar ductitis, and emphysema (BADE) in industrial machine-manufacturing workers. Am J Ind Med. 2019;1-11. https://doi.org/10.1002/ajim.23038; with permission.)

styrene exposure in epidemiologic studies reflect the effects of another toxin that shares styrene's exposure profile. Planned studies using a novel humanized mouse model that accounts for differential styrene metabolism in mice and humans should better inform our understanding of bronchiolitis in this industry.

We recently reported a novel form of bronchiolitis among workers at a facility making industrial machines.[92] Five relatively young never-smoking men had clinical presentations notable for insidious post-hire onset of cough, wheeze, and exertional dyspnea; airflow obstruction and reduced diffusing capacity; and radiologic centrilobular emphysema. Expiratory imaging was available for 2 patients, which demonstrated air trapping consistent with obstructive small airways disease. Histopathology in all cases was notable for a unique pattern of B-cell bronchiolitis, alveolar ductitis, and emphysema ("BADE") (**Fig. 1**).[92] The findings were distinct from recognized diseases such as hypersensitivity pneumonitis, obliterative bronchiolitis, and follicular bronchiolitis. Clinical outcomes included chronic dyspnea, progressive functional decline, and lung transplantation in 1 patient to date.

The cause of this novel occupational bronchiolitis is uncertain.[92] The 5 BADE cases occurred in production workers who had multiple potential exposures including metals (mainly steel and aluminum), VOCs primarily associated with painting, and aerosols related to metalworking fluids. Air sampling for metals and VOCs demonstrated low exposures, but 2 endotoxin samples exceeded the Dutch exposure limit,[93] indicating potential to impair respiratory health. The evident source of endotoxin was aerosolization of metalworking fluid, which was heavily colonized by the gram-negative bacteria *Pseudomonas pseudoalcaligenes*; indeed, the facility's most commonly used metalworking fluid was reportedly designed, through its constituents, to promote the growth of this organism.[94] In the absence of certainty about the cause of BADE, we recommended precautionary measures to limit exposures and periodic spirometry to monitor the workforce for functional declines that would merit further evaluation. Multidisciplinary investigation of additional BADE cases or clusters could help to illuminate the cause and guide preventive strategies.

Other notable recent reports of occupational bronchiolitis include a small airways-centered granulomatous reaction in 4 workers chronically exposed to polytetrafluoroethylene (PTFE or Teflon) and acute fibrosing bronchiolitis in a construction worker 1 week after substantial dust and mold exposure.[95–97] In one of the PTFE cases, an extensive workplace exposure assessment concluded the disease was caused by aerosolization of PTFE during spray coating of frying pans.[97] The construction worker's histopathologic findings and robust response to steroids were reminiscent of the classic descriptions from the mid-20th century of proliferative bronchiolitis from oxides of nitrogen in silo-fillers' disease, highlighting the value of historical experience to our understanding of novel disease.[98]

SUMMARY

Occupational bronchiolitis is a heterogeneous set of lung conditions that affect the small airways and can occur following a range of inhalation exposures related to work. The most common clinical presentation is progressive and unexplained exertional dyspnea. Health care providers should maintain a high index of suspicion for bronchiolitis caused by occupational exposures in any patient who presents with chronic, progressive, and unexplained exertional dyspnea. Both current and past occupational exposures should be considered, including prior military deployment–related exposures. Patients being evaluated for potential bronchiolitis should undergo diagnostic testing that allows for an assessment of the small airways, which could include HRCT and possibly lung biopsy.

DISCLOSURE

The authors have nothing to disclose. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

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