World Trade Center Asthma

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Introduction

More than 40,000 men and women were exposed to products of combustion and particulate matter as a result of the terrorist attacks on the World Trade Center (WTC) on September 11, 2001 [1]. Pulverization of the structural components of the towers released a plume of dust and ash into lower Manhattan and beyond. The dust was a complex mixture of over 400 substances including glass fibers, asbestos, silica, lead, polycyclic aromatic hydrocarbons, metals, and polychlorinated biphenyls [2] with a particulate matter concentration of 100,000 mg/m [3]. In addition, prolonged smoldering fires [4] emitted gaseous and particulate combustion products. Exposures were ongoing for hundreds of thousands of people who lived, worked, or volunteered in the area since recovery and cleanup efforts took 9.5 months to complete [4]. Multiple studies have reported increased rates of asthma as well as worsening of preexisting asthma in those exposed [4–9]. Although most of the particulate matter was expected to deposit in the upper airway, it is clear that lower airway deposition and injury occurred. Longitudinal studies have demonstrated persistent airway hyperresponsiveness (AHR) years after the attacks. This chapter discusses the following aspects of WTC asthma: epidemiology, pathogenesis and risk factors, clinical presentation and comorbidities of disease, as well as a multidisciplinary approach to management.

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WTC Asthma Epidemiology

It is difficult to clearly define the scope of WTC asthma prevalence. Symptom-based surveys have identified increased incidence of self-reported asthma for 18 months following the attack [10]. A WTC registry of rescue and recovery workers ($n = 25,748$) documented self-reported post-9/11 asthma in 926 workers for a 3-year incidence rate of 3.6%, or 12 times higher than that expected for the general adult population [11]. Increased incidence of new-onset asthma has been associated with the time of arrival at the site, cumulative exposure, and lack of appropriate respiratory protections [12]. Twenty seven percent of New York City residents reported increased asthma symptoms in the weeks after the disaster [13] although it is not clear how many of these individuals had pre-existing asthma.

Pathogenesis

WTC asthma is a distinct entity that arose in individuals exposed to products of combustion and particulate matter following the collapse of the towers on 9/11. Although most of the particulate matter (>90%) was >10 μm [2] and expected to deposit mainly in the upper airways, mouth breathing and alkalinity of the material impaired nasal clearance. Analyzed samples were highly alkaline, with a pH > 10. WTC responders breathed at high minute ventilations where mouth breathing predominates [6]. Though only a small percentage of particles were <10 μm (i.e., respirable fraction), the enormity of the dust cloud still led to significant exposure for many individuals. Induced sputum testing in a sample of highly exposed NYC firefighters has demonstrated WTC dust in the lower airways measuring >10 μm [14].

WTC asthma is part of the spectrum of disorders ranging from reactive airways dysfunction syndrome (RADS) that involves an acute high-level irritant exposure to irritant-induced asthma with recurrent lower-level exposures [5, 6, 15]. The mechanism of injury is believed to be non-immunologic [16, 17]. Asthma symptoms are due to direct airway epithelial damage with release of pro-inflammatory mediators [18]. Pathologic changes of the airways include denuded epithelium, submucosal chronic inflammation, and focal thickening of the basement membrane [19]. The inflammatory process of irritant-induced asthma is not thought to be primarily Th2 cell mediated [20]. In a mouse model, acute exposure to high levels of WTC particulate matter induced mild pulmonary neutrophilic inflammation and marked AHR to inhaled methacholine [21]. Interestingly, Kazeros et al. reported peripheral eosinophilia that correlated with persistent wheeze and airflow obstruction in WTC disaster-exposed residents and workers [22]. Although eosinophilia is generally thought typical of Th2-related inflammation, asthma is phenotypically heterogeneous, and a “low Th2” lymphocyte/eosinophil cohort has been described based on analysis of bronchial epithelial cells [22, 23]. Induced sputum analysis in a study of 39 WTC firefighters revealed rising neutrophil and eosinophil counts with increasing

work duration [14]. In the same study, sputum analysis also revealed elevated metalloproteinases (MMP)-9 levels in WTC firefighters [14]. Metalloproteinases (MMPs) are also thought to play a role in the airway remodeling of asthma and in the induction of AHR [24].

Nolan et al. [3] demonstrated that elevated granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage-derived chemokine (MDC) were associated with subsequent increased risk of airflow obstruction in WTC disaster-exposed firefighters with normal pre-September 11, 2001, forced expiratory volume in 1 s (FEV_1), suggesting that such inflammatory biomarkers were important in the pathogenesis of asthma post-9/11. Others have shown that human bronchial epithelial cell produce GM-CSF in response to particulate matter [25, 26] and that MDC is elevated in the bronchoalveolar lavage fluid of asthmatic patients. Different WTC-related exposures and individual susceptibility to exposure (lower baseline lung function) may have influenced the levels of these biomarkers and their physiologic impact.

Regardless of the predominant inflammatory cellular subtype and the cytokine milieu, the consequences of allergic asthma and irritant-induced asthma are the same with AHR and airflow obstruction with or without reversibility [16, 17]. It is possible that WTC asthma is phenotypically heterogeneous although this is not yet known.

Risk Factors

Risk factors for the development of WTC asthma relate predominantly to the magnitude of irritant exposure.

A clear exposure-response gradient exists, with most severe asthma symptoms in those directly exposed to the dust cloud on the morning of 9/11 [27–29]. In a prospective cohort study, airway hyperreactivity at 1, 3, and 6 months was associated with exposure intensity (evaluated by self-administered questionnaires), independent of ex-smoking and airflow obstruction [27]. At 6 months after collapse of the towers, highly exposed workers (on site on the morning of day 1) were 6.8× more likely than moderately exposed workers (arrived on the afternoon of day 1 or during day 2) and controls (workers absent from the site during the first 2 weeks or longer) to be hyperactive [27]. Each additional month of work increased the likelihood of respiratory symptoms by 8–11% [30], although the effect on new-onset asthma is not specifically known.

Risk factors associated with an increased incidence of WTC asthma are shown in Table 1. Among WTC workers who arrived at the disaster site on 9/11/01, increased time to mask or respirator use was associated with a greater risk for the development of asthma [11]. In one study of 1660 individuals with high-intensity exposure (arriving on the morning of the collapse of the towers) at the WTC site, only 22% of workers reported frequent mask use [31]. In another study, respirators were worn rarely or not at all by 93% on the day of the collapse, 85% on the day after, and 76%

Table 1 Risk factor for WTC asthma

Increased incidence of WTC asthma associated with:
Dust cloud exposure on the morning of 9/11
Earlier arrival time relative to collapse
Work on the "pile"
Cumulative exposure (particularly >90 days)

Adapted from [11]

on the second through sixth days after the attack [29]. There were multiple reasons for lack of respirator use including lack of adherence and availability of masks for many responders [31].

In some reports, the workers' role at the site was a risk factor for new-onset asthma. This was particularly true for firefighters, who had heavier dust exposures than other workers. The significance of these reports was enhanced by the availability of lung function and methacholine bronchoprovocation data that preceded the exposure [8, 31]. Although there are many reports of respiratory symptoms in multiple other rescue/recovery workers, volunteers, lower Manhattan residents, and office workers, these do not specifically link the symptoms to new-onset asthma [31–34].

Smoking status was an additive risk factor for WTC asthma [5]. Other reports on irritant-induced asthma demonstrate that tobacco use at the time of inhalational resulted in lower FEV_1 and FEV_1/FVC, as well as in increased AHR [5, 18, 35, 36].

Preexisting atopy can predispose individuals to develop irritant-induced asthma in general [18], though this was not clearly demonstrated in the WTC population [37]. In fact, the atopy prevalence in this WTC population was similar to that of the general US population [37].

Age may have also influenced the risk of new onset asthma in those with WTC exposure, but data on this are limited.

Clinical Presentation

Upper and lower respiratory symptoms were common in individuals exposed at the WTC disaster [4–7, 28, 29, 38, 39]. In most cases, the onset of symptoms consistent with asthma began within 6 months following irritant exposure at the WTC site [5]. Individuals diagnosed with WTC asthma presented similarly to the general asthma patient with chest tightness, exertional and non-exertional dyspnea, wheezing, and cough [29]. Diurnal variation of symptoms and sensitivity to fumes, weather extremes, and other classic asthma triggers are common. Patients typically complain of nighttime awakenings with asthma that is not ideally controlled. One unique clinical feature of this population was the "WTC cough," described as persistent cough syndrome recurring during the 6 months after 9/11. WTC cough was associated with underlying airway inflammation and symptoms of rhinosinusitis,

bronchitis, and GERD [29]. Workers with preexisting asthma may have experienced greater severity of asthma symptoms than controls [7].

Multiple studies have evaluated lung function in those exposed at the WTC disaster, but not all of these individuals carry the diagnosis of asthma [1, 3, 28, 31, 40, 41]. Although an obstructive pattern is described, other studies have reported a restrictive pattern with or without air trapping [40]. In the setting of small airway obstruction, forced expiratory maneuvers may result in bronchial collapse and cessation of airflow. The airways that close off at a higher than normal closing volume during the maneuver do not contribute to the full vital capacity or to FEV_1 after closing volume is reached, resulting in a proportional drop in forced vital capacity (FVC) and FEV_1 [42]. This allows for a maintained FEV_1/FVC ratio and explains the restrictive pattern [43, 44].

AHR and variable response to bronchodilator has also been demonstrated [1, 8, 27, 29]. In fact, Banauch et al. found that AHR developing shortly after the WTC attacks predicted RADS at 6 months in highly exposed workers (present within 2 h of the towers' collapse) [27] (Fig. 1).

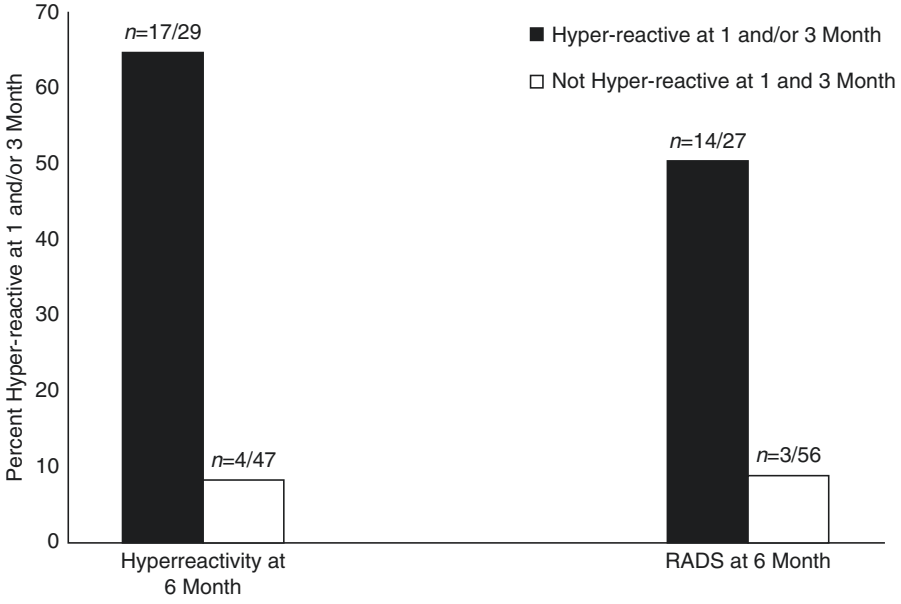

Fig. 1 Highly exposed subjects who were hyper-reactive at 1 or at 3 months were more often hyper-reactive at 6 months. Highly exposed subjects who were hyper-reactive at 1 or at 3 months had RADS (defined as both symptomatic and hyper-reactive) at 6 months significantly more often ($p = 0.021$) than those who were not hyper-reactive. Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society [27]. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

Interestingly, many individuals had normal spirometry despite significant respiratory symptoms, which may point to a lack of sensitivity of spirometry to fully demonstrate abnormalities of airway function [28, 45]. In a study of ironworkers exposed at the WTC disaster, lung function abnormalities were far more evident by forced oscillometry (FO) testing than by spirometry [28]. Similarly, while spirometric response to bronchodilator was variable, there was a higher prevalence of bronchodilator response as assessed by FO [28, 46]. FO has shown correlation between asthma symptoms and isolated small airways dysfunction even in the setting of normal spirometry [47]. FO evidence of small airway disease, possibly at the level of the terminal bronchiole, has been an important finding and may be a key characteristic of asthma in the WTC population [28, 46, 48].

Chest imaging is not typically used to diagnose asthma (unless utilized to exclude other entities), but it has played a larger role in WTC patients and has been correlated with physiologic data. Inspiratory and expiratory chest CT findings may demonstrate air trapping and bronchial wall thickening [49, 50]. Though not diagnostic, this may help support a diagnosis of asthma in cases where clinical symptoms are consistent.

Comorbidities

Comorbidities that impacted the presentation of asthma were common in those exposed at the WTC disaster. There was an increased prevalence of chronic rhinosinusitis in those with highest WTC dust exposure (reactive upper airway dysfunction syndrome (RUDS)) [6]. One study of 1138 rescue/recovery workers and volunteers found 92% had new or worsened ear, nose, and throat symptoms [11], including nasal congestion/drip, sore throat, and sinusitis.

Gastroesophageal reflux disease was found in up to 45% of FDNY rescue workers between 1 and 6 months after collapse, with higher rates in those with bronchial hyper-reactivity [27]. Also, in a survey of 332 firefighters with WTC cough, 87% reported heartburn, often with findings of laryngopharyngeal reflux disease [5, 29]. GERD was associated with spirometric abnormalities and with a diagnosis of WTC-related lower airway disease [51]. It is unclear if GERD is a cause, effect, or complication of asthma, but concurrent treatment is essential to optimize asthma control.

Increasing WTC exposure was associated with a trend toward more severe obstructive sleep apnea (OSA) [52], although further studies are necessary to confirm this association. Additionally, a significant relationship exists between OSA and poorly and very poorly controlled asthma [53]. Treating OSA can improve asthma symptoms in individuals with concurrent OSA [54] although we are not aware of any studies demonstrating this in WTC patients.

COPD was also seen in those exposed at the WTC disaster. This is particularly important since individuals may have the asthma-COPD overlap syndrome.

Extensive review of available literature did not reveal any data in the WTC population, but this is a particularly challenging comorbidity as irreversible airway obstruction can make treatment less effective. It was suspected when fixed obstruction, hyperinflation, decreased diffusion capacity, and/or emphysematous changes on CT were present in individuals who smoked cigarettes [5].

Post-traumatic stress disorder (PTSD) was experienced by many who were exposed to the WTC attacks. PTSD may considerably impact the individual's as well as the healthcare worker's perception of respiratory symptoms, thereby delaying or confounding the diagnosis of asthma and treatment [10, 53].

Diagnostic Evaluation of WTC Asthma

As with traditional asthma, the diagnosis of WTC-related asthma should be suspected in patients with typical respiratory symptoms provoked by classic triggers. Differential diagnosis includes chronic obstructive pulmonary disease (COPD), bronchitis, bronchiectasis, bronchiolitis, hyperventilation/panic attacks, chronic sinusitis, GERD, vocal cord dysfunction, recurrent respiratory infections, and heart disease [55]. It is important to assess for comorbidities that can worsen asthma symptoms, contribute to the pathophysiology of the disease, and influence treatment response [56].

Clinical evaluation should include a focused history and physical exam, detailed assessment of clinical symptoms, occupation and WTC-related exposure history (e.g., arrival time, exposure time, work performed, and use of respirator) (Fig. 2).

Diagnostic challenges in this population include the fact that (1) multiple comorbidities may impact the presentation, (2) the spirometric pattern may not be typical for asthma (i.e., restrictive pattern or isolated small airways dysfunction) [5, 28, 40, 46], and (3) bronchial hyper-reactivity may be intermittent or disappear in irritant-induced asthma with time after exposure removal [4, 57].

Treatment of WTC-related asthma should follow the same guidelines for asthma patients in general [54, 58]. Inhaled corticosteroid therapy is the cornerstone of asthma therapy for symptom control. Short-acting beta agonists are used as rescue medications. Importantly, treatment of WTC asthma patients involves limiting irritant exposure and addressing the multiple physical and mental health comorbidities that often coexist and can decrease asthma control. There is a dose-response relationship with the number of mental health conditions (PTSD, depression, and generalized anxiety disorder) and poorer asthma control [53]. Specialists from allergy and immunology, gastroenterology, otolaryngology, occupational and environmental medicine, and psychiatry must work together with pulmonologists and primary care practitioners to manage WTC-related asthma. Various multidisciplinary treatment centers exist in the tri-state area and function in such a capacity to provide individualized diagnostic and management services to this population.

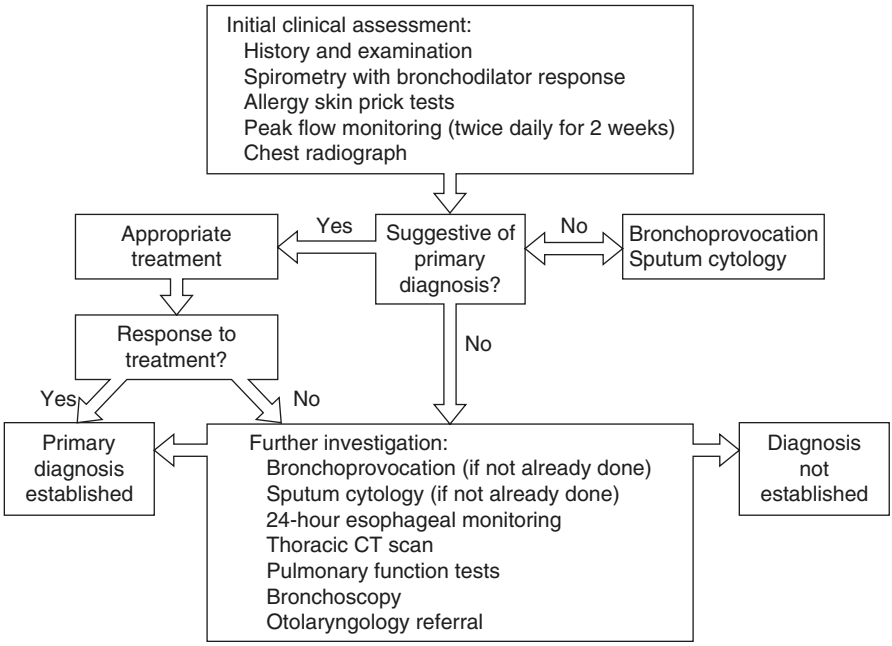

Fig. 2 Algorithm for the diagnostic evaluation of lower respiratory symptoms among former World Trade Center workers and volunteers [4]

Longitudinal Follow-Up and Prognosis of WTC Asthma

There have been multiple studies demonstrating decline in lung function in individuals exposed to WTC dust [1, 12, 31, 48]. Skloot et al. found high rates of abnormal spirometric indices (particularly a low FVC) among non-FDNY workers [1]. Although the majority of the cohort manifested normal decline of lung function between baseline and follow-up (about 3 years later), a small percentage were rapid decliners, losing >300 mL/year of FVC [1]. Aldrich et al. also discovered initially decreased FEV_1 values in its firefighter and EMS workers, with ongoing lung function decline from 2002 to 2008 [12]. The firefighters had an average decline in FEV_1 of 600 mL during this 6-year period [12]. In individuals with persistent lung function decline, it is possible that airway inflammation may progress to remodeling [12]. This may also explain why AHR can continue after termination of exposure in spite of appropriate therapy [8].

Since many responders were previously healthy and fit, a greater loss of function may be required before pulmonary function tests appear abnormal. For those workers without pre-9/11 spirometric data, identifying and treating asthma may be particularly challenging.

In conclusion, asthma continues to be a significant problem in individuals exposed to particulate matter as a result of the WTC disaster. Although some have improved, others have persistent and often difficult-to-control lower respiratory symptoms. The impact of comorbidities on WTC asthma is substantial. As the WTC-exposed population ages, the structural and functional changes of the lung associated with normal aging (i.e., mechanical changes resulting in decreased airway caliber and decreased airflow) may lead to more severe asthma in those affected. Since the trajectory of lung function decline in WTC asthma over many years is not yet known, continued long-term monitoring is imperative to effectively evaluate and manage this population.

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