

REVIEW



Irritant-induced asthma

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Purpose of review

To describe the recent insights into the definition, causes, natural outcome, and key elements of irritant-induced asthma (IIA) management.

Recent findings

IIA is a subtype of occupational asthma without immunologic sensitization and includes the typical reactive airway dysfunction syndrome (RADS) and a more gradual form called not-so-sudden IIA, when onset of asthma follows repeated low-dose exposure to irritants. The World Trade Center tragedy brought new insight in the understanding of IIA, suggesting that it can exhibit a prolonged interval between exposure and recognition of clinical symptoms and disease. Dimethyl sulfate has been recently reported to cause RADS and repeated diesel exhaust exposure to cause not-so-sudden IIA in patients who worked in a bus garage. Cleaning workers who are exposed to a large variety of irritants and sensitizers are especially at risk of occupational asthma and IIA.

Summary

IIA includes RADS and not-so-sudden IIA. Outcome of IIA is as poor as occupational asthma with sensitization. Treatment of IIA does not differ from standard asthma treatment, but high-dose vitamin D could be assessed further for possible therapeutic benefit.

Keywords

irritant-induced asthma, reactive airways disorder syndrome, World Trade Center

INTRODUCTION

In 2008, the ACCP (American College of Chest Physician) published their updated state-of-the-art consensus statement on the 'Diagnosis and Management of Work-Related Asthma' [1]. Work-related asthma can be divided in two major entities shown in Fig. 1 [2]. The term occupational asthma encompasses all workers who develop new respiratory symptoms and obstructive airways physiology consistent with the diagnosis of asthma, and the cause can be directly attributed to an exposure in the workplace. The key element is that occupational asthma is asthma caused by exposure(s) to an organic protein, chemical, or other compound that is unique to the workplace. Occupational asthma is further split into two subtypes – sensitizer-induced occupational asthma (>90% of the cases) and irritant-induced asthma (IIA) that includes reactive airway dysfunction syndrome (RADS). Work-exacerbated, or work-aggravated, asthma (WEA) refers to previously diagnosed asthma that is worsened, but not caused, by agents found in the workplace. The distinction between these two entities is not superfluous as

it impacts treatment strategies and medicolegal decisions.

DEFINITION OF IRRITANT-INDUCED ASTHMA

IIA also referred to as 'asthma without latency' [3] is a type of work-related asthma in which there is no recognized latency and no immunologic sensitization [1,4]. According to Lemièr *et al.* [5], the definition of IIA is limited to an asthmatic syndrome from single or multiple exposures to irritant products. When only a single exposure is responsible, the term RADS is used [6]. Brooks and Bernstein [7] described the case definition of the

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KEY POINTS

- Irritant-induced asthma (IIA) is an important subtype of occupational asthma.
- IIA can onset after repeated low-dose exposure to irritants at work.
- Frequent reported agents are cleaning materials; chemicals; chlorine; solvents; acids, bases, oxidizers, smoke; and diesel exhaust.
- Research is still needed to improve the management and outcome of IIA.

term RADS that is the result of an acute, excessive, singular exposure to a specific agent generally at work. When onset of asthma is not sudden but follows repeated low-dose exposure to one or more bronchial irritants, various names have been proposed for this phenotype of IIA: low-dose reactive airways dysfunction syndrome [8], not-so-sudden IIA [9], and low-intensity chronic exposure dysfunction syndrome (LICESDS) [3]. More recently, the term irritant-induced occupational asthma with latency has been proposed by Burge *et al.* [10]. A retrospective analysis of 86 asthmatic patients performed by Brooks *et al.* [4] identified 54 patients discerned to have IIA. From this analysis, there are two distinct clinical scenarios emerging; the first group (29 patients) developed sudden-onset asthma that was analogous to RADS. Clinical manifestations began immediately or within a few hours (always within 24 h) following a single, massive exposure, usually accidental in origin. In contrast, the onset of asthma in the second group (25 patients) was not so sudden, and the causative irritant exposure was not brief; it was often not massive and continued for more than 24 h, and initiation of asthma took longer to evolve. Host predisposition seemed

operative in the not-so-sudden, IIA cases. Forty percent of the participants were documented to have asthma in remission. Thus, some patients with assumed new-onset asthma were actually persons with preexisting asthma clinically quiescent for at least 1 year before the exposure. Almost 90% of individuals with not-so-sudden asthma were shown to be atopic. It appeared that IIA occurring after more moderate or 'tolerable' exposures required a host susceptibility to be present. The diagnosis of not-so-sudden IIA may be difficult to establish when the irritant exposure is of moderate intensity or intermittent in nature. Clinicians have to make all attempts to identify a reason for why asthma develops in the individual. This means there is careful evaluation for preexisting susceptibility factors, especially asthma in remission. Diagnostic criteria for RADS are as follows (data from [7]).

- (1) Absence of preexisting respiratory disorder, asthma symptoms, or a history of asthma in remission; and exclusion of conditions that can simulate asthma.
- (2) Onset of asthma after a single exposure or accident.
- (3) Exposure to irritant vapor, gas, fumes, or smoke in very high concentrations.
- (4) Onset of asthma occurs within minutes to hours and always less than 24 h after the exposure.
- (5) Findings of a positive methacholine challenge test (<8 mg/ml) following the exposure.
- (6) Possible airflow obstruction on pulmonary function testing.
- (7) Another pulmonary disorder to explain the symptoms and findings is excluded.

CAUSE

Extensive lists of agents associated with RADS have been published [3,11]. The seven most frequently reported agents for work-related RADS were, in decreasing order: cleaning materials; chemicals not otherwise specified (nos); chlorine; solvents nos; acids, bases, oxidizers nos, smoke nos; and diesel exhaust. The responsibility of repeated exposure to occupational irritants in the pathogenesis of new-onset asthma has been demonstrated or suggested by several epidemiological studies or case reports [3]. These publications especially concern workers exposed to chlorine gas in pulp mills and paper mills, meat wrappers, workers exposed to formaldehyde, aluminum smelters exposed to pot fume emissions containing gaseous fluorides, hydrofluoric acid, and sulfur dioxide (potroom asthma), or workers exposed to machining fluids.

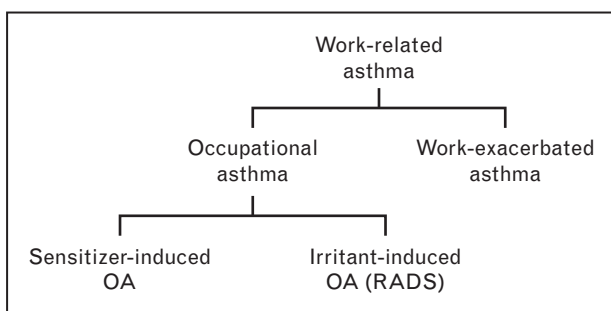


FIGURE 1. Classification scheme for the major types of asthma in the workplace. This scheme is based on the American College of Chest Physicians 2008 guidelines and is adapted with permission [1]. Reproduced from [2].

SPECIFIC CAUSES

Cleaning agents and asthma

This problem has been recently reviewed by Quirce and Barranco [12[•]]. Cleaning workers are exposed to a large variety of cleaning products containing both irritants and sensitizers; thus, the onset or aggravation of asthma in this group could be related to an irritant-induced mechanism or to a specific sensitization. The main sensitizers contained in cleaning products are disinfectants, quaternary ammonium compounds (such as benzalkonium chloride), amine compounds, and fragrances. The strongest airway irritants in cleaning products are bleach (sodium hypochlorite), hydrochloric acid, and alkaline agents (ammonia and sodium hydroxide), which are commonly mixed together. Exposure to the ingredients of cleaning products may give rise to both new-onset asthma, with or without a latency period, and WEA. High-level exposure to irritants may induce RADS. Cleaning workers may also have a greater relative risk of developing asthma because of prolonged low-to-moderate exposure to respiratory irritants.

Diesel exhaust exposure

Accidental large acute exposure to diesel exhaust has been reported to cause acute IIA or RADS. Adewole *et al.* [13] have recently reported cases of occupational asthma or low-dose IIA attributed to diesel exhaust. The 15 cases came from the SHIELD database, a surveillance scheme for occupational asthma in the West Midlands, UK [14]. In three of them, there was objective confirmation of occupational asthma from nonspecific reactivity to methacholine and serial peak expiratory flow (PEF) measurements at work. All the three workers worked in bus garages where diesel buses were run indoors, engine tuning was done in the main garage, and rolling roads were present for servicing and testing running buses. The three patients had wheezing and breathlessness, which started for the first time while working on buses indoors, with improvement on days off and on holidays. The three workers were on inhaled corticosteroids. Diesel exhaust was the only identified exposure. All had new-onset asthma with long latent intervals from first exposure to first symptom, without any large acute exposure. They therefore do not fulfill the criteria for acute IIA but fulfilled the criteria for the diagnosis of not-so-sudden, IIA [9,15^{••}]. Some clinicians would argue that the differential diagnosis in these three patients will include new-onset asthma with WEA from diesel exposure.

Dimethyl sulfate

Dimethyl sulfate (DMS) is an oily liquid used as a solvent, stabilizer, sulfonation agent, and catalyst. Aghabiklooei *et al.* [16] described the first RADS case related to this cause after accidental exposure to the vapor of DMS. The patient was a healthy 29-year-old man who was referred to the emergency department of Firouzgar hospital after accidental exposure to the vapor of DMS while transporting a broken bottle containing it. The patient had opened the windows but had continued working in the same place for another 6 h. He did not mention any history of atopy. At presentation, he was completely awake with the complaint of dyspnea, dry cough, photophobia, and hoarseness. Redness of the pharynx, conjunctivitis, and cholinergic signs and symptoms (including miosis, diaphoresis, coryza, and lacrimation) were evident. On physical examination, generalized wheezing was auscultated all over the lungs. The patient was admitted to the intensive care unit, he improved with conservative treatment and was discharged after 9 days; however, exertional dyspnea, wheezing, and thick white sputum persisted and therefore, RADS related to DMS vapor was confirmed and the patient was treated with prednisolone. Exertional dyspnea continued up to 10 months. Hoarseness lasted for 6 months. This case shows that DMS vapor inhalation can cause RADS, especially in the chemical workers who continue working in the contaminated place despite the relatively good air conditioning.

The World Trade Center tragedy and irritant-induced asthma

It has been estimated that more than 50 000 people worked on the rescue and recovery effort that followed destruction of the WTC on 11 September 2001. WTC rescue and recovery workers were exposed to a complex mix of airborne contaminants. Collapse of the towers pulverized building materials and created a dense cloud of dust which was found to consist predominantly of coarse particles and contained cement, glass fibers, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and polychlorinated furans and dioxins [17]. The WTC dust was highly alkaline (pH 9.0–11.0) and consequently irritant. Despite the fact that the majority of particles were greater than 10 μ m in diameter, the dust burden on day 1 was so high that a substantial number of particles in the respirable range was present and inhaled into the small airways, as demonstrated by induced sputum analysis in firefighters exposed to WTC dust [10,18]. A high prevalence of lower airway disease (LAD) symptoms was reported by

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several early surveys. Following a variety of symptom-based survey reports, a clinical characterization of the presumed WTC-related occupational respiratory diseases categorized the chronic airway diseases as IIA, chronic nonspecific bronchitis, chronic bronchiolitis/small airway disease, and aggravated preexistent chronic obstructive lung disease (most frequently chronic obstructive pulmonary disease, but also asthma) [19–21]. Notably, very few cases presented as acute or short-latency IIA (or RADS). A recent publication summarized the short-term and medium-term lower respiratory health effects observed in these workers [22]. Risk factors for WTC-related LAD included early (on 11 September or 12 September 2001) arrival at the WTC site and work at the pile of the collapsed towers. The bronchial inflammatory effects seemed largely independent of susceptibility factors like atopy, but were affected to some degree by previous or current smoking habits, differential exposure to inhalants, and, in a good number of cases, confirmed or suspected preexisting respiratory disease [19]. A major contribution of this experience to the understanding of work-related asthma was the demonstration that IIA can exhibit a prolonged interval between exposure and recognition (by either patients, physicians, or both) of clinical symptoms and disease. In the vast majority of workers, lower respiratory symptom onset was relatively delayed and insidious over weeks and months, and in some patients latency between exposure cessation and symptom onset could be up to 6 months after leaving the disaster site. That interval can be related to the relatively low proinflammatory potential of the WTC dust, as evidenced in experimental animals [22]. Furthermore, only about 27% of the patients with LAD had evidence of nonspecific bronchial reactivity 1–2 years after leaving the WTC site, although that may partly reflect the well known resolution or mitigation of nonspecific bronchial hyperreactivity that can happen in some individuals [22]. The WTC exposure incident underscored the need for careful attention to occupational hazards in disaster situations. Despite their relative low toxicity in experimental animal studies, which may explain the prolonged exposures and slow development of respiratory symptoms among workers, the inhaled toxicants demonstrated a potential to affect the entire airways.

OUTCOME

The fate of patients with IIA is often considered to be poor, but there are very few surveys of prognosis in patient cohorts. Where such information is available, it suggests that many patients find that their

symptoms respond poorly to standard asthma medications [23]. A recent publication has suggested that the long-term outcome of patients with IIA is at least as poor as that found in patients with sensitizer-related occupational asthma [24]. In this cohort of 35 patients with RADS in which the causal agent was chlorine in 20 cases (57%), after a minimum interval of 4 years and an average of around 13 years, almost all 35 patients continued to have symptoms consistent with asthma, a third were using inhaled corticosteroids. There was little evidence of any improvement – or deterioration – in spirometry, the mean percentage predicted FEV1 and FVC values being approximately 70% at diagnosis and follow-up. Twenty-three patients had repeat measurements of their metacholine responsiveness, seventeen (74%) with persistently abnormal results. In the same cohort, Malo also reported the type of causal agent (chlorine vs. others), the interval since the accident, and a visit to an emergency room or a hospitalization did not influence the prognosis. However, being a smoker at the time of the inhalational accident resulted in lower airway caliber at follow-up, which might suggest that smoking plays an additive role. In a prospective study of 3 years' duration in workers exposed to 'puffs' of chlorine, Gautrin *et al.* [25] had already showed that smoking and the number of 'puffs' of chlorine exerted a significant additive effect on the diminution in airway caliber and on the increase in responsiveness with time. Being older and having greater hyperresponsiveness at the time of the accident were associated with the absence of recovery or improvement in PC20 at the follow-up. Having a lower PC20 at the time of diagnosis and a longer duration of exposure with symptoms are also generally associated with a worse prognosis in the case of sensitizer-related occupational asthma [6].

Cullinan [26] in a related editorial noticed that the levels of anxiety and depression in the cohort reported by Malo *et al.* [24] were quite high and raises the question of whether, how, and when psychological treatment might be helpful in improving symptomatic recovery.

MANAGEMENT

Because RADS is usually precipitated by an unforeseen industrial accident, removal of the worker is automatic. Emergency treatment might require inhaled beta2 agonists, systemic steroids, and oxygen depending on the severity. Once the acute episode has been managed appropriately, treatment of the ongoing asthmatic situation using a combination of inhaled corticosteroid and bronchodilators

is mandatory. Long-term inhaled corticosteroids may be appropriate in reducing the severity of nonspecific bronchial hyperresponsiveness (NSBH) [27]. Reduction of exposures to workplace irritants, passive smoking, vehicle emissions, outdoor pollutants, and temperature or humidity extremes is also important [3]. Unfortunately, many patients with RADS find that their symptoms respond poorly to standard asthma medications [23]. Varney *et al.* [28] described the first use of high-dose vitamin D in a patient with RADS who was refractory to conventional treatments. The presence of vitamin D receptors in the airways and their capability to inhibit proinflammatory cytokines might explain the improvement in this case and may be consistent with a questioned role for vitamin D deficiency in asthma causation [29].

CONCLUSION

IIA is a subtype of occupational asthma without immunologic sensitization that includes two entities: the typical RADS and a more gradual form called the not-so-sudden IIA; in that case, onset of asthma follows repeated low-dose exposure to irritants. The WTC tragedy brought new insight into the understanding of IIA; in some circumstances, IIA can exhibit a prolonged interval between exposure and recognition of clinical symptoms and disease. Cleaning workers who are exposed to a large variety of irritants and sensitizers are especially at risk of occupational asthma and IIA. Outcome of IIA is as poor as occupational asthma with sensitization. Actually, treatment of IIA does not differ from standard asthma treatment.

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None.

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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