Clinical Management Review

Irritant-Induced Asthma

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Irritant-induced asthma (IIA) is a phenotype of asthma caused by the inhalation of irritant agents. Definite, probable, or possible IIA have been described, depending on the concentration of the inhaled irritants and the onset of respiratory symptoms respective to the time of exposure. Definite IIA represents approximately 4% to 14% of all cases of new-onset work-related asthma. Agents responsible for IIA can be encountered as fumes, gases, aerosols, or dusts. The most frequent are chlorine, nitrogen oxides, sulfur dioxide, ammonia, acetic acid, solvents, and cleaning materials. Although the diagnosis of definite IIA is based on a suggestive clinical history along with evidence of reversible airflow limitation and/or nonspecific bronchial hyperresponsiveness, possible IIA cannot be diagnosed with certainty because the relationship between exposure and the onset of symptoms is difficult to establish. This article reviews the epidemiology, pathophysiology, diagnostic approach, and management of IIA. **(J Allergy Clin Immunol Pract 2022;10:2799-806)**

Key words: *Irritant-induced asthma; RADS; Asthma; Irritant agents*

INTRODUCTION AND DEFINITIONS

In 1985, Stuart Brooks and colleagues[1] described the occurrence of asthma-like symptoms in 10 previously healthy individuals within 24 hours of exposure to high levels of irritant vapors, fumes, or smoke. They labeled this condition reactive airways dysfunction syndrome (RADS) and proposed clinical criteria for its diagnosis.

Since this first description, many cases of asthma induced by a variety of exposures to different irritants agents have been reported. In recent years, it has been recognized that RADS was one phenotype of a broader condition called irritant-induced asthma (IIA).

The European Association of Allergy and Clinical Immunology[2] described three phenotypes of IIA according to the levels and type of exposure to irritant agents.

Definite IIA relates to acute-onset IIA manifested by the rapid onset of asthma within 24 hours of a single, very high-intensity exposure to an irritant compound (similar to the original RADS phenotype).

Probable IIA is the development of asthma after multiple symptomatic moderate- to high-level exposures to irritants.

Possible IIA is the delayed development of asthma after chronic or repeated exposure to low to moderate levels of irritant substances. Possible IIA has been described based on epidemiologic findings.

Irritant-induced asthma is a difficult condition to study owing to its acute nature and the often long delay between exposure and the initial consultation. The literature describing this condition is scarce and mainly consists of descriptive studies. The current document is intended to help clinicians investigate and treat AII according to current knowledge.

EPIDEMIOLOGY

There is scarce information on the burden of IIA in the general population.[3,4] Acute-onset IIA accounted for 4% to 14% of all cases of new-onset work-related asthma reported to notification schemes of occupational respiratory diseases in various countries worldwide.[5-10] A follow-up study conducted among participants in the European Community Respiratory Health Survey documented that the incidence of self-reported symptomatic acute inhalation was associated with an excess risk for new-onset asthma (3.8%), compared with individuals without an acute inhalation event (0.9%; risk ratio = 3.33; 95% confidence interval [CI], 1.00-11.13).[11] However, reporting bias might have affected these findings, because individuals with asthma-related symptoms at the time of the baseline survey were more likely to report inhalation incidents 9 years later.[12] A similar study conducted among participants in the European Community Respiratory Health Survey in five Northern Europe countries also found that a history of "accidental peak exposure to irritants" was associated with an increased likelihood of physician-based new-onset asthma in men (hazard ratio = 2.4; 95% CI, 1.3-4.7),[13] but the characteristics of these peak exposures were not detailed. A cross-sectional questionnaire study of Estonian adults revealed a significant association (odds ratio = 1.88; 95% CI, 1.48-2.37) between physician-based asthma and workplace exposure to "low-to-moderate levels of irritants," as assessed by an asthma-specific job exposure matrix.[14]

A number of workforce surveys documented an increased likelihood of adult-onset asthma among workers who experienced repeated symptomatic accidental inhalation exposures (gassings) to chlorine,[15] ozone,[16] and sulfur dioxide[17] in various

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Abbreviations used
AHR- Airway hyperresponsiveness
cysLTs- Cysteinyl leukotrienes
ICS- Inhaled corticosteroids
IIA- Irritant-induced asthma
RADS- Reactive airways dysfunction syndrome
WTC- World Trade Center

industries. Associations between chronic workplace exposure to moderate levels of irritants and an increased risk for asthma were reported among workers involved in welding, aluminum production, wood manufacturing, and farming and dairy activities.[4] The most convincing evidence supporting the role of chronic moderate irritant exposures in the development of IIA was provided by epidemiologic studies of workers exposed to disinfectant and cleaning products. Population and workforce-based studies consistently reported an increased prevalence and incidence of asthma among professional cleaners and health care workers, although the precise causal exposures accounting for the increased incidence of asthma in these workforces have not been clarified.[18,19] Some of these studies identified cleaning materials that typically contain a mixture of chemicals with respiratory irritant properties (eg, bleach, ammonia, degreasing sprays, decalcifiers), but some ingredients such as quaternary ammonium compounds may induce asthma through a presumably sensitizing mechanism.[20,21]

Exposure to airborne dust and various pollutants after the collapse of the World Trade Center (WTC) towers on September 11, 2001 and during the recovery operations has been associated with increased rates of new-onset asthma.[22] The rate of symptomatic asthma among WTC responders increased from 0.2% (95% CI, 0.1% to 0.2%) in 2000 to 8.2% (95% CI, 6.8% to 9.8%) in 2005, and slightly decreased between 2005 and 2007 (7.8%; 95% CI, 6.9% to 8.7% for the latter).[23] The age-adjusted standardized morbidity ratio (1.7; 95% CI, 1.6-1.8) for symptomatic asthma among WTC responders was elevated in 2002 to 2005 and did not change afterward. Compared with 2000 (before September 11, 2001), the risk for symptomatic asthma was about 40-fold higher among WTC responders.

PATHOLOGY AND ANIMAL MODELS OF IIA

Case series have described pathologic changes in the airways at different stages after exposure to inhaled irritants.[24,25] After the initial epithelial shedding accompanied by a fibrinohemorrhagic exudate in the submucosa within 3 days after exposure, subepithelial edema and signs of regeneration of the epithelial layer with proliferation of basal and parabasal cells appeared within 2 months after exposure. In addition, bronchoalveolar lavage revealed neutrophilia in the acute stage of acute IIA. Pathological samples from subjects with IIA taken as long as 19 years after the inhalation accident showed signs of airway remodeling with increased thickness of the basement membrane and persistent airway inflammation.[26]

Several experimental studies and case reports in both animal models and humans have also explored the effects of chlorine exposure on the respiratory system.[27-30] Initial chlorine exposure generally induces an influx of inflammatory cells such as neutrophils, lymphocytes, eosinophils, and macrophages into the airways. In addition, epithelial apoptosis and necrosis and airway hyperresponsiveness (AHR) can occur.[30,31] Acute chlorine exposure also induces epithelial cell damage in mouse models.[31]

Not only might exposure to chlorine induce direct oxidative epithelium injury in mice, further damage may occur with the migration and activation of inflammatory cells such as neutrophils within the airway epithelium, with the subsequent release of reactive oxygen species and proteolytic enzymes. The release of reactive oxygen species can contribute to airflow limitation and airway hyperreactivity.[32] Exposure to lower levels of chorine can also be detrimental when airway epithelium is already damaged. In a mouse model with airway epithelial damage, low-dose chlorine exposure led to airway barrier impairment and the development of airway hypersensitivity.[33] This suggests that airway epithelial damage may be a risk factor for developing IIA in case of reexposure to irritant agents.

In addition to the production of reactive oxygen species, chlorine exposure induces the production of cysteinyl leukotrienes in a concentration-dependent fashion.[34] Furthermore, cysteinyl leukotriene-1 receptor modulates airway inflammation and dysfunction after pulmonary oxidative injury caused by chlorine inhalation.

Figure 1 proposes potential pathophysiologic mechanisms of AII based on evidence from animal models.

These important observations have led to potential therapeutic avenues tested in animal models. The administration of an antioxidant after chlorine exposure mitigated the occurrence of AHR or airway inflammation in mice. The metalloporphyrin catalytic antioxidant AEOL10150 administered 1 and 9 hours after chlorine exposure in mice limited the occurrence of AHR, airway inflammation injury-induced airway epithelial cell regeneration, and oxidative stress.[35] Furthermore, administration of the leukotriene receptor antagonist montelukast before chlorine exposure prevented the occurrence of AHR and neutrophilic airway inflammation induced by chlorine exposure in mice, probably through IL-6—dependent mechanisms.[36] However, these findings remain to be tested in humans. These studies were performed after chlorine exposure. The efficacy of such treatments after exposure to other types of irritants is uncertain. The mechanisms of injuries induced by other types of irritants have not been studied as deeply.

CAUSES AND RISK FACTORS

A wide variety of agents inhaled as fumes, gases, aerosols, or dusts have been associated with the development of acute IIA (ie, onset after a single exposure) and subacute IIA (ie, onset after multiple exposures) in case reports and a few case series (Table I).[5,37-40] The most common agents involved in acute IIA were chlorine, nitrogen oxide, sulfur dioxide, ammonia, acetic acid, solvents, and cleaning materials.[5,37,40] In a series of acute and subacute IIA diagnosed at the Finnish Institute of Occupational Health in 2000 to 2018, 57% of cases were attributable to strongly acidic or alkaline chemicals.[40] Medical surveillance of rescue workers involved in the WTC disaster provided consistent evidence that high levels of airborne alkaline dust (pH 9.5-11) and products of combustion or pyrolysis were able to induce IIA that developed insidiously over a few days to months after the massive exposure.[41,42]

Although IIA refers to asthma caused by inhalation exposure to agents that act as respiratory irritants in the absence of immunologically mediated sensitization, low—molecular weight

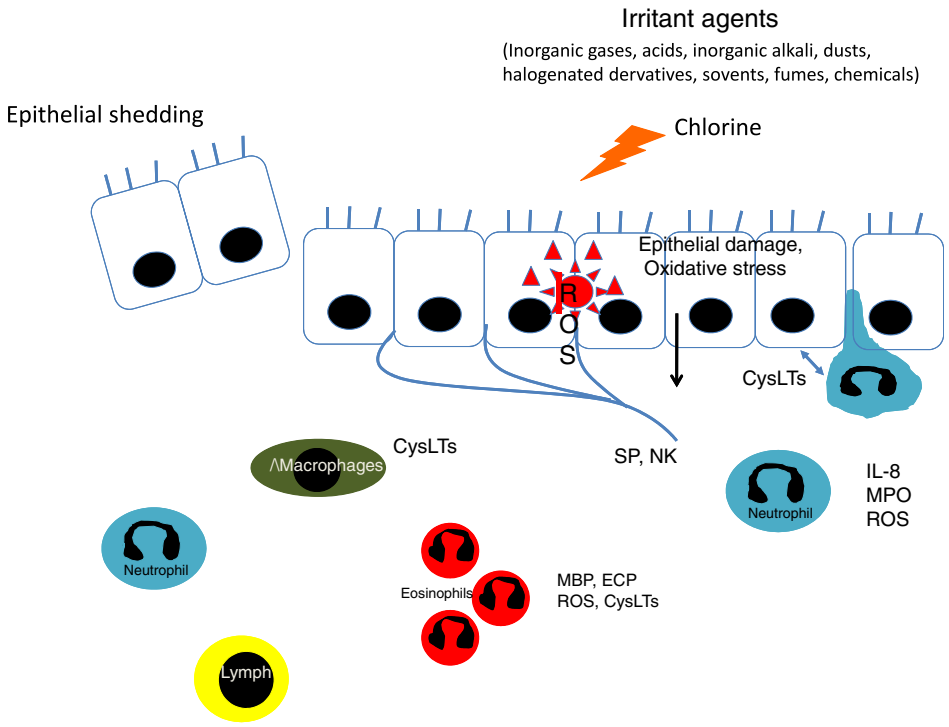

FIGURE 1. Suspected pathophysiologic mechanisms of irritant-induced asthma (IIA). Chlorine exposure induces an influx of inflammatory cells such as neutrophils, lymphocytes, eosinophils, and macrophages into the airways. It also induces epithelial cell damage. Chlorine can induce direct oxidative epithelium injury, but further damage may also occur with migration and activation of inflammatory cells such as neutrophils within the airway epithelium, with subsequent release of reactive oxygen species (ROS) and proteolytic enzymes. In addition to the production of ROS, chlorine exposure induces the production of cysteinyl leukotrienes (cysLTs). *ECP*, eosinophilic cationic protein; *MBP*, major basic protein; *MPO*, myeloperoxidase; *NK*, neurokinins; *SP*, substance P.

chemicals with a known sensitizing potential have been documented to cause acute IIA.[37,43]

Typically, exposures leading to acute IIA are caused by spills of volatile compounds, the accidental release of chemicals under pressure, overheating of materials, accidental fire with the release of complex mixtures of thermal degradation products, and mixing cleaning products.[40,44-46] The effects of these exposures are often amplified by reduced ventilation in a confined space. Interestingly, the Finnish study mentioned earlier found that acute IIA occurred after inhalation accidents at work in many different types of occupations and resulted mainly from a lack of information and insufficient guidance of the workers, whereas subacute IIA occurred predominantly among industrial operators and maintenance workers performing their usual work tasks under poor work hygiene conditions.[40]

Conceivably, the airway response to irritants is determined by the intensity and duration of exposure, the physicochemical properties of inhaled agents (eg, the vapor pressure and solubility), the intrinsic chemical reactivity of the substance, and host susceptibility.[46] Water-soluble compounds and particles with an aerodynamic diameter of more than 5 μm are predominantly deposited in the upper airways, whereas water-insoluble agents and particles of 0.5 to 5 μm can reach the distal airways. However, the environmental and host factors that determine the initiation and persistence of IIA remain largely uncertain because most reports of IIA lack quantitative assessment of the causal exposure. Qualitative assessment of exposure to a spill of acetic acid by industrial hygienists provided evidence of a dose—response relationship between the level of exposure and the prevalence of AHR.[47] Also, rescue workers involved in the WTC disaster who were highly exposed (ie, within 2 hours of collapse) were 6.8 times more likely (95% CI, 1.8-25.2) than were moderately exposed workers to exhibit AHR 6 months after the collapse and 19 times more likely to experience respiratory symptoms in conjunction with AHR (95% CI, 4.8-76.1).[42] A follow-up survey of pulp mill workers repeatedly exposed to high levels of chlorine found that the severity of gassing incidents, as evidenced by hospital emergency room visits, was a more significant risk factor for the persistence of AHR than was the number of incidents.[48]

On the other hand, host factors, such as smoking and atopy, have not been consistently associated with the development and persistence of acute and subacute IIA.[42,47-50]

CLINICAL EVALUATION

Inhalation of a high concentration of irritant agents causes the occurrence of sudden respiratory symptoms (eg, dyspnea, cough, wheezing, chest tightness) typically within 24 hours of exposure, as originally described by Brooks et al.[1] Coughing is usually the most prominent symptom reported by patients. Eight percent of firefighters who arrived at the scene during the collapse of the WTC towers on September 11, 2001 developed a severe and

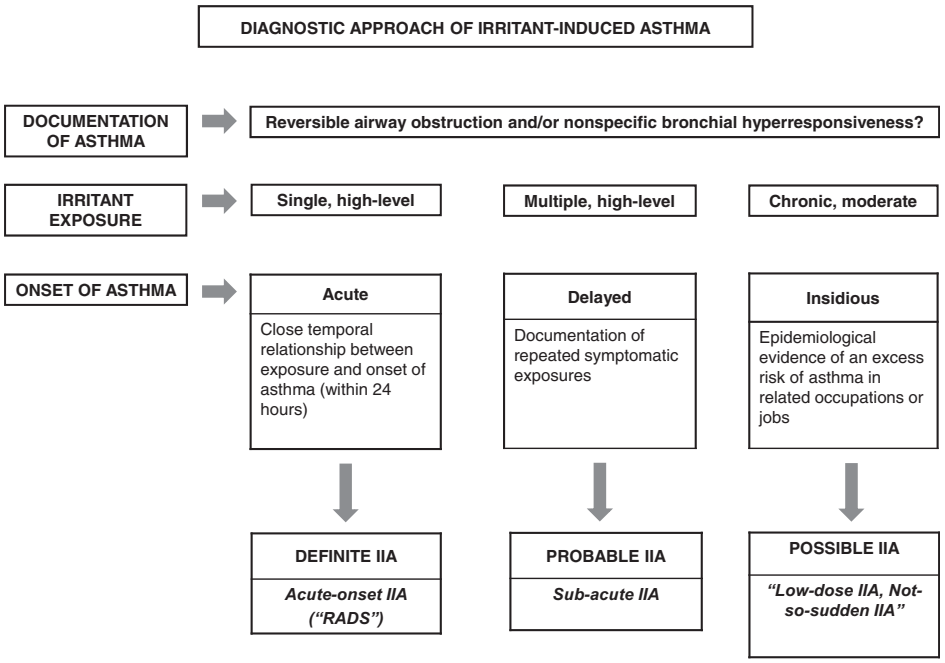

FIGURE 2. Diagnostic approach for irritant-induced asthma (IIA). *RADS*, reactive airways dysfunction syndrome.

persistent cough.[41] This observation was confirmed in a recent retrospective Finnish study.[51]

Some subjects exposed to a high concentration of irritant agents also report a burning sensation in the throat and or nose, described as reactive upper airway dysfunction syndrome.[52] In contrast, subjects exposed to repetitive lower concentrations of irritant exposures may be unaware of the multiple exposures and may report episodic symptoms not precisely linked to known exposures. Conjunctivitis, pharyngeal erythema, tearing, tachypnea, and wheezing have been documented after acute exposures to irritant agents.[48,53]

The assessment of a patient suspected of having IIA should include a thorough clinical history including the time of onset of respiratory symptoms respective to the occurrence of the acute exposure, especially when the assessment takes place weeks or months after the initial exposure.

Although a chest radiograph is often performed to investigate potential noncardiogenic pulmonary edema, pneumonia, or other causes of dyspnea, it is not normally useful to diagnose IIA. Although high-resolution computed tomography is not required to make a diagnosis of IIA, high-resolution computed tomography obtained in 29 symptomatic rescue and recovery workers at the WTC site showed air trapping, based on a mosaic pattern on the end-expiratory images in 25 of these workers.[54]

Laboratory testing is not contributive to diagnose IIA, but a complete and differential blood cell count may be helpful to discard other diagnoses in a patient reporting sudden dyspnea.

Spirometry pre-administration and post-administration of bronchodilators should be performed to document airflow limitation and assess its reversibility. Airway obstruction is generally less reversible in acute IIA compared with asthma.[55] A restrictive pattern that is likely to represent a manifestation of a small-airway disease has also been observed.[54,56]

In case of a normal spirometry, airway responsiveness should be assessed by a methacholine or histamine inhalation challenge test, especially in patients who are seen weeks or months after the initial exposure.

Fractional exhaled nitric oxide is not increased months after diagnosis of IIA,[51] but it has not been measured immediately after the occurrence of the offending exposure.

Specific inhalation challenges are not useful for diagnosing IIA because this is not an allergic disorder that causes the disease. However, some agents such as isocyanates have both irritant and sensitizing properties. Some patients exposed to high concentrations of isocyanates developed both RADS and occupational asthma (OA) to those agents.[57] In such instances, specific inhalation challenges may be conducted to diagnose OA. Table II summarizes the diagnostic tests used to diagnose IIA.

The diagnosis of acute-onset IIA is based on the combination of a suggestive exposure history, a suggestive time course of symptom onset respective to the occurrence of exposure, and evidence of reversible airflow limitation and/or nonspecific bronchial hyperresponsiveness in the absence of an alternative diagnosis. Criteria originally published by Brooks et al[1] were adapted by the European Association of Allergy and Clinical Immunology in 2014 (Table III).

Probable IIA is more difficult to diagnose because often no single exposure is responsible for the occurrence of respiratory symptoms. Therefore, the relationship between multiple exposures and the onset of symptoms is more difficult to establish. However, a history of multiple exposures to irritant agents combined with the presence of asthma-like symptoms, and the presence of reversible airway limitation and/or hyperresponsiveness are suggestive of the diagnosis.

Possible IIA can be suspected, but the relationship between exposure and the onset of symptoms is difficult to establish.

TABLE I. Examples of exposures involved in acute and subacute irritant-induced asthma

Chemical category	Examples of chemicals
Inorganic gases	Chlorine (eg, pulp mills or released by mixing sodium hypochlorite with acids), chloramines released by mixing sodium hypochlorite with ammonia, sulfur dioxide, nitrogen oxides, ozone
Inorganic acids	(Per)acetic (disinfectant), sulfuric, hydrochloric, hydrofluoric (thermal degradation product of fluorinated hydrocarbons), and hydrobromic acids
Inorganic alkali	Ammonia, sodium hydroxide, hydrazine
Inorganic dusts	Calcium oxide (lime) and cement (eg, World Trade Center dust)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), heated fluorinated hydrocarbons (cooling agents; thermal degradation into hydrofluoric acid), orthochlorobenzylidene malononitrile (tear gas)
Solvents	Perchloroethylene
Fumes	Diesel exhaust, fire smoke, paint and urea fumes, fumes of iodine and aluminium iodide, dimethylaminoethanol (corrosion inhibitor)
Mixtures of chemicals	Cleaning agents (bleach, ammonia, detergents, degreasing sprays, decalcifiers, disinfectants)
Potential respiratory sensitizers	Isocyanates (eg, thermal degradation of polyurethane insulation materials), aldehydes, phthalic anhydride

TABLE II. Diagnostic tests to conduct in patient suspected of having IIA

Diagnostic tests	Results
Chest x-rays	Not contributive to diagnosis of IIA but can discard other diseases
High-resolution computed tomography	Not contributive to diagnosis of IIA but may be useful to discard other disease. Can show mosaic pattern in end-expiratory images in IIA
Complete blood count	Not contributive for diagnosis of IIA but can discard other diseases
Spirometry pre- and post-bronchodilator	Reversible airflow limitation. Restrictive pattern in some cases
Methacholine inhalation challenge test	Airway hyperresponsiveness
Specific inhalation challenges	Not contributive to diagnosis of IIA but can be useful to diagnose occupational asthma in patients exposed to agents with both irritant and sensitizing properties

IIA, irritant-induced asthma.

Epidemiologic studies have identified occupations with an increased risk for asthma, such as cleaners[58] or pulp mill workers.[59] Although these studies can be used to support a diagnosis of IIA in a patient with similar exposures, distinguishing IIA caused by repeated moderate- or low-level exposures from coincidental non—work related asthma is difficult and often impossible in clinical practice. Figure 2 shows the diagnostic approach for IIA.

OUTCOME

There is still limited information on the outcome of acute inhalation incidents. Malo et al[60] evaluated changes in AHR in 51 pulp mill workers who had experienced a symptomatic chlorine gassing episode. Twenty-nine of these workers (57%) showed significant AHR 1.5 to 2 years after the inhalation incident.[48] Reevaluation 1 year later of 18 of the 29 subjects with AHR at initial assessment revealed that six (33%) showed significant improvement in AHR, including five subjects for whom the level of airway responsiveness to methacholine was no longer in the asthmatic range.[60] These data indicated that AHR can improve and even resolve over a few years after an acute symptomatic inhalation accident. However, a recent retrospective study of 69 workers with the diagnosis of acute (n = 30) or subacute (n = 39) IIA at the Finnish Institute of Occupational Health[51] showed that the short-term outcome of IIA evaluated 6 to 8 months after the diagnosis was worse than that of subjects with sensitizer-induced OA. At the follow-up assessment, 68% of subjects received high-level treatment (ie, Global Initiative for Asthma step 4 or 5), 30% used a short-acting β_2-agonist daily, and 24% reported at least one severe exacerbation since the initial evaluation. Compared with sensitizer-induced OA, those with IIA exhibited poorer asthma control, as evidenced by an Asthma Control Test score of 19 or less (odds ratio [OR] = 3.94; 95% CI, 1.50-10.35) as well as higher rates of high-level treatment (OR = 2.24; 95% CI, 1.16-4.33) and exacerbations (OR = 4.22; 95% CI, 1.67-10.67). Interestingly, the outcomes of acute and subacute IIA were similar, but acute IIA was associated with a higher risk for severe exacerbations (OR = 11.68; 95% CI, 2.62-52.08).

The long-term outcome of acute-onset IIA was investigated in 35 subjects reassessed at a mean interval of 14 years (range, 4-24 years) after the onset of IIA.[61] At follow-up, all subjects reported respiratory symptoms and 68% were treated with inhaled corticosteroids (ICS). Airway hyperresponsiveness persisted in about three-quarters of subjects, although it was improved in 39%. Airway obstruction was not significantly improved; mean FEV_1 was 74.5% of predicted value at baseline and 69.5% at follow-up. Only 17% of subjects recovered from asthma with normal spirometry and AHR at follow-up. Notably, sputum eosinophilia greater than 2% was documented in 22% of subjects. These findings indicate that the long-term functional outcome of acute-onset IIA is similar to what has been described in subjects with sensitizer-induced OA after cessation of exposure to the causal agent.[62]

Longitudinal studies of WTC rescue and recovery workers have provided new insights into the functional outcome after massive exposures to a complex mixture of dusts and combustion

TABLE III. Diagnostic criteria for diagnosing acute-onset irritant-induced asthma

Absence of preexisting asthma symptomatology
Onset of asthma symptoms after single specific inhalational exposure or accident
Presence of airflow limitation with significant bronchodilator response or nonspecific bronchial hyperresponsiveness to histamine or methacholine
Exposure to irritant vapor, gas, fume, or smoke at very high concentration
Onset of asthma symptoms within minutes to hours and <24 h after exposure
Exclusion of other pulmonary disorders that can explain symptoms or simulate asthma

products. Six months after the WTC disaster, AHR persisted in 55% of rescue workers who showed AHR at assessments performed 1 or 3 months after the collapse.[42] Aldrich et al[63] conducted a follow-up study of 173 firefighters with normal spirometry and no asthma history before the WTC terrorist attacks who had completed a methacholine challenge test within 2 years after the event. Significant AHR was documented in 16% of participants at baseline assessment in 2001 to 2003 and persisted in 57% of them at follow-up in 2013 to 2014. Airway hyperresponsiveness at follow-up was associated with an estimated 15.4 mL/y greater FEV_1 decline compared with rescue workers without AHR at follow-up.

MANAGEMENT OF ACUTE-ONSET IIA

Published data on the management of IIA are scarce, mainly related to case reports of acute-onset IIA. Emergency treatment might require inhaled β_2-agonists, systemic and/or ICS, and oxygen, depending on the severity at the time of the incident. Once the acute phase has been managed appropriately, subjects should be assessed as early as possible to determine the presence of airflow limitation and/or AHR. Subjects with persistent asthma should be treated according to current clinical practice guidelines. It is unclear whether some subgroups of patients such as smokers or patients with childhood asthma who experience AII should be managed differently. The current management is based on changes in respiratory function along with the symptoms experienced by patients.

Based on animal studies and a few case reports,[25,64] it seems that treatment with systemic and/or inhaled steroids after the accident is beneficial, but the optimal pharmacologic treatment of IIA has not been assessed by clinical trials. Instead, it was developed according to a pragmatic approach proposed by expert clinicians. Subjects with IIA seem to require more asthma medications than do those with OA.[51]

Pharmacologic treatment of IIA

Bronchodilators. β_2-Agonists or anticholinergic agents are usually administered to patients with airflow limitation based on the severity of symptoms.

Systemic corticosteroids. Systemic corticosteroids have been administered to patients presenting with acute IIA with moderate to severe symptoms. Although this approach has not been validated in clinical trials, animal model data have shown improvement in lung resistance and hyperresponsiveness after a week of treatment given after acute exposure.[64]

Inhaled corticosteroids. Inhaled corticosteroids have been proposed in patients who have a documented irritant exposure with mild initial symptoms and mild airflow limitation. Normalization of AHR was reported after treatment with ICS in subjects exposed to chlorine.[25]

The optimal dose of ICS has not been determined. It is usually based on the symptoms of patients, their functional impairment, and their response to treatment. The weaning of ICS depends on the evolution and may require long-term therapy. The timing of ICS initiation had no effect on asthma outcomes or lung function parameters in the Finnish cohort of acute and subacute IIA.[51] In a follow-up study of WTC firefighters, corticosteroid therapy was associated with an estimated 13-mL/y lower FEV_1 decline over the follow-up but did not affect the change in AHR.[63]

Leukotriene receptor antagonists. A mouse study showed that pretreatment with montelukast, a leukotriene receptor antagonist, prevented the occurrence of AHR and the increase in pulmonary neutrophilia and eosinophilia after exposure to chlorine.[36] However, this effect has not been investigated in humans or reported in subjects with IIA. Furthermore, montelukast has not been tested with other types of irritant agents besides chlorine.

Nonpharmacologic management

Patients with IIA who are not sensitized to workplace agents often can continue to work in the same environment with appropriate pharmacologic treatment, measures to prevent further high-level exposure to irritants, and regular medical assessment, including measurements of AHR.[65]

The management of IIA should also address potentially associated disorders, such as chronic rhinitis (ie, reactive upper airways dysfunction syndrome),[66] vocal cord dysfunction,[67] perceived intolerance to multiple chemicals, and posttraumatic stress disorder,[22,68,69] which can result from accidental exposure to irritant substances, enhance the clinical expression of respiratory symptoms, and complicate the medical management.

PREVENTION

The primary prevention of acute IIA relies mainly on the correct labeling and hazard statement of potentially irritant agents as well as the education of workers to ensure understanding of potential irritant exposure, safe handling, and mixing of chemicals, the appropriate use of personal protective equipment, and measures to be taken in the event of an accident at work. When an accidental exposure has occurred, it is important to investigate the reasons for the event and to implement measures to prevent a further similar accident.

Prevention of subacute IIA implies eliminating airborne irritant products when possible and controlling exposures to safe levels by occupational hygiene measures such as containment, adequate ventilation, exposure level monitoring with alarm systems, and use of respiratory protective equipment. The

potency of airborne sensory irritants can be quantified through a computerized, reproducible test based on changes in respiratory pattern induced by increasing concentrations of chemical irritants in nonanesthetized mice that may help to determine occupational exposure limits in humans.[70]

CONCLUSION

Irritant-induced asthma is a condition that is probably overlooked. Although epidemiologic studies clearly show that chronic exposure to low doses of irritant agents causes an excess of incident asthma cases, attributing the causality of those cases to the occupational environment with certainty is almost impossible in clinical practice.

Many questions remain unanswered. The optimal treatment of AII has not been identified. Although ICS seems to be beneficial, no clinical trial has compared this treatment with placebo. The effects of antioxidants or leukotriene receptor antagonists after acute exposure to irritant agents have not been studied in humans. Whether employing biomarkers after exposure to a high concentration of irritants may be useful to choose the best treatment has not been studied. Future research, although challenging to undertake, will have to focus on these issues.

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