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EAACI POSITION PAPER: IRRITANT-INDUCED ASTHMA

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LIST OF ABBREVIATIONS

IIA: Irritant-induced asthma
NSBH: Non-specific bronchial hyperresponsiveness
OA: Occupational asthma
RADS: Reactive airways dysfunction syndrome

TRP: Transient receptor potential

ABSTRACT

The term irritant-induced (occupational) asthma (IIA) has been used to denote various clinical forms of asthma related to irritant exposure at work. The causal relationship between irritant exposure(s) and the development of asthma can be substantiated by the temporal association between the onset of asthma symptoms and a single or multiple high-level exposure(s) to irritants, whereas this relationship can only be inferred from epidemiological data for workers chronically exposed to moderate levels of irritants. Accordingly, the following clinical phenotypes should be distinguished within the wide spectrum of irritantrelated asthma: 1) definite IIA, i.e. acute-onset IIA characterized by the rapid onset of asthma within a few hours after a single exposure to very high levels of irritant substances; 2) probable IIA, i.e. asthma that develops in workers with multiple symptomatic high-level exposures to irritants; and 3) possible IIA, i.e. asthma occurring with a delayed onset after chronic exposure to moderate levels of irritants. This document prepared by a panel of experts summarizes our current knowledge on the diagnostic approach, epidemiology, pathophysiology, and management of the various phenotypes of IIA.

INTRODUCTION

It is currently acknowledged that the term “occupational asthma” (OA) refers to the initiation of asthma or the recurrence of previously quiescent asthma caused by either immunological sensitization to a specific substance at work (i.e., high-molecular-weight [glyco]proteins or low-molecular-weight chemicals), which is termed “immunologic/allergic OA” or “OA with latency” or “sensitizer-induced OA”, or by exposure to inhaled irritants at work, which has been labelled “non-immunologic/non-allergic OA” or “OA without latency” or “irritant-induced (occupational) asthma, IIA” [1-5]. The term “irritant-induced (occupational) asthma” (IIA) has been introduced to characterize the development of asthma symptoms, non-specific bronchial hyperresponsiveness (NSBH), and airway inflammation induced by irritant mechanisms, as opposed to OA caused by immunologic mechanisms leading to specific bronchial hypersensitivity to a workplace agent. However, the term IIA has been often loosely used to denote various forms of asthma related to irritant exposures at work.

The objective of the present Task Force was to propose an operational classification and a practical diagnostic algorithm of IIA based on the clinical features, exposure characteristics, and the level of evidence supporting the causal relationship between asthma and exposure to irritants at work, and to summarize the available information on the pathogenesis, epidemiology and management of the various phenotypes of IIA. The current literature (bibliographic search strategy available as online material) was critically reviewed by a panel of experts and a consensus was reached through an informal iterative process during four meetings. Although upper and lower airways are closely related, the effects of irritant exposures on the nasal mucosa are not specifically considered in this document since they have been extensively

addressed in recent reviews [6-8]. The resulting document is primarily aimed to assist clinicians who are faced with the diagnosis and management of this still poorly characterized condition.

HISTORICAL PERSPECTIVE

In 1985, Brooks and co-workers proposed the term “reactive airways dysfunction syndrome” (RADS) to describe the sudden onset of asthma within a few hours after a single high-level exposure to irritating vapours, fumes or smoke [9]. Tarlo and co-workers later introduced the term "irritant-induced asthma" to characterise workers who develop asthma after either single or multiple high-level irritant exposures [10]. Expert authors formally acknowledged that “IIA or RADS, which may occur after a single or multiples exposures to nonspecific irritants at high concentrations” should be considered a form of OA and designated as “OA without a latency period” [1] or “nonimmunologic OA” [3]. A number of authors proposed to extend the concept of RADS to the progressive/delayed onset (or even the reactivation) of asthma in workers with “moderate” and persistent exposure to irritants at work [11-16]. More recently, the American College of Chest Physicians guidelines recommended that the term IIA should be used to include “Cases that do not meet these stringent criteria [i.e. the criteria of RADS] (eg, where there is a lag of several days before the onset of symptoms, or when there is no single massive exposure but rather repeated exposures over days or weeks, less
massive exposures, or a shorter duration of symptoms) [4].

CLINICAL PHENOTYPES OF IRRITANT-INDUCED ASTHMA

The clinical features and exposure characteristics of published clinical reports of IIA, as well as the evidence supporting causality, were critically analyzed in order to disentangle the various clinical phenotypes that have been subsumed under the umbrella term of “IIA”.
Noteworthy, distinguishing the phenotypes of IIA according to the characteristics or the intensity of irritant exposure (e.g. relative to permissible exposure limits) [17], is somewhat arbitrary since estimation of the exposure intensity has been most often qualitative, based on history and experience, and not on measurements of actual levels of irritant compounds generated during inhalation accidents.

Reactive airways dysfunction syndrome or acute-onset irritant-induced asthma

RADS is characterized by the onset of asthma symptoms within 24 hours after a single, most often accidental, high-level exposure to irritant substances in subjects without pre-existing asthma. Although widely used, the denotation RADS is poorly indicative of the nature and mechanisms of the disorder, so this Task Force suggests that it should be replaced by "acute-onset IIA" [2, 18] to avoid further confusion with delayed or progressive forms of asthma associated with chronic irritant exposures. Brooks and co-workers proposed stringent clinical and functional criteria for the diagnosis of acute-onset IIA (Table 1) [4, 9]. It is now widely accepted that this syndrome is the most definitive form of asthma induced by respiratory irritants [1-5]. Numerous different agents have been associated with the development of acute-onset IIA (Table 2) [19, 20]. It is expected that IIA may be induced by any high-level exposure to fumes, gases, sprays, or even dusts having irritating properties. Typically, the exposure is caused by spills of volatile compounds, accidental release of irritants under pressure, accidental fire with release of complex mixtures of

thermal degradation products, or inadvertent reduction of ventilation rate in a confined space [21]. The very strict criteria for RADS originally set by Brooks and co-workers specified that the symptoms should persist for more than three months [9]. However, there is evidence that asthma symptoms and NSBH can resolve over a few weeks after an inhalation incident [22, 23]. There was a consensus among the Task Force members that asthma symptoms and NSBH should persist for more than a few weeks for establishing a diagnosis of acute-onset IIA, although any precise cut-off would be arbitrary and has not been retained in later versions of the published criteria for RADS [4, 21]. Most published case reports of acute-onset IIA concerned subjects who underwent “massive” exposure to irritants leading to respiratory symptoms severe enough to require hospitalization or at least acute medical care. In such settings, the causal role of the irritant exposure can be ascertained with a high level of confidence by the strong temporal association between an inhalation accident and the rapid onset of asthma symptoms. However, the few available case series describing subjects who fitted the operational definition of acute-onset IIA after a single high-level exposure to a spill of acetic acid in a hospital [24], to methyl isothiocyanate released after the derailment of a train [25], or to a complex mixture of alkaline dust and combustion products after the World Trade Centre disaster [26-28], indicated that the condition can also occur after an acute exposure that did not cause very severe respiratory symptoms and can even develop insidiously over a few days to months after the massive exposure [25-28]. Noticeably, a number of reports outlined an association between upper and lower airways symptoms after high-level accidental exposures, giving rise to the concept of “reactive upper airways dysfunction syndrome” (RUDS) [29] or “acute irritant-induced rhinitis” [6].

Multiple high-level exposures

Clinical reports have described the development of asthma in subjects exposed to multiple high-level exposures, though less clearly massive than in acute IIA. Tarlo and co-workers [10] reported on ten subjects who developed asthma after one or more high-level exposures to various irritant compounds. The delay between the exposure(s) and the onset of symptoms and the severity of the symptoms were not detailed. Chan-Yeung and co-workers described three pulp mill workers who had a history of repeated “gassing” episodes, among which some were severe enough to require medical care [30]. They developed asthma “shortly” after one of the severe episodes. Thus, in some subjects with a history of multiple high-level exposures, the clinical picture is very similar to “acute-onset IIA”, the symptoms occurring shortly after one severe inhalation incident. In other subjects with repeated highlevel exposures, the onset of symptoms may be more insidious. IIA has been documented after repeated high-level exposures (i.e., “puffs” or “gassings”) to irritants substances, mainly chlorine, SO_2, and ozone (Table 4) [10, 30-34]. The causal relationship of this form of IIA occurring with a less acute onset in a context of multiple high-level exposures can be supported by the documentation of repeated symptomatic inhalation accidents requiring medical care or reports to first aid units or occupational health services. In such settings where the onset of symptoms is less abrupt than in the classical description of Brooks and co-workers, the term “sub-acute IIA” would be more appropriate.

Chronic exposure and delayed-onset asthma

Several publications have described the onset of asthma or even the reactivation of quiescent asthma in workers with repeated, chronic exposure to "moderate" levels of one or more respiratory irritants at work that were not considered accidental or unusual. Various names have been proposed for this clinical phenotype: "low-dose/low intensity IIA/RADS" [11], "not-so-sudden RADS" [12], "low intensity chronic exposure dysfunction syndrome" [35], "IIA with latency" [16], or simply "IIA" [13-15]. The main clinical and exposure characteristics of reported cases are summarized in Table 3 [11-16]. These cases involved individuals in whom asthma had a delayed onset after repeated, often daily, exposure to "moderate", although poorly documented, concentrations of irritant compounds in the workplace. The subjects presented with heterogeneous clinical features. The pattern of work-related asthma symptoms and the changes in lung function tests at work were often consistent with both OA and work-exacerbated asthma. In the majority of reported cases, the evidence supporting the work-relatedness of asthma relied on the following criteria: 1) adult onset of asthma (or reactivation of previously quiescent asthma [12]); (2) chronic exposure to irritants; and (3) absence of an identified sensitizer in the subject's working environment. Accordingly, the causal relationship between workplace irritant exposure and the development of asthma was weak on an individual basis.

Accidental aggravation of asthma

Although the diagnostic criteria for acute-onset IIA stipulate that this condition can be considered only in subjects without pre-existing asthma [4, 9], some case reports strongly suggest that a single acute inhalation exposure to irritants may lead to a persistent reactivation of asthma in remission or a persistent aggravation of a previously stable asthma [36-38]. Chatkin and co-workers introduced the term "accidental aggravation of asthma" for describing the worsening of asthma symptoms following an acute accidental exposure to respiratory irritants in workers with a previous history of asthma [22]. Whether such "accidental aggravation of asthma" should be categorised as acute-onset IIA or as a form of "work-exacerbated asthma" [39] still remains debatable. There was a consensus among Task Force members to consider such cases as acute-onset IIA when asthma is totally quiescent before the acute irritant exposure (e.g., asymptomatic and without medication for at least one year [12]) and as work-exacerbated asthma when the disease is clinically active before the incident.

EPIDEMIOLOGICAL EVIDENCE FOR IRRITANT-INDUCED ASTHMA

Epidemiological studies typically have a different focus than clinical studies. Specific phenotypes of IIA are often not identified, but asthma prevalence or incidence is compared between groups of exposed and non-exposed individuals. Few epidemiological surveys have addressed asthma due to single, high-level exposures (Table 4). In the longitudinal European Community Respiratory Health Survey it was found that retrospectively reported acute inhalations were associated with new-onset asthma [40]. A more detailed analysis in this population showed that reporting bias could not be discarded; individuals with any respiratory problems at baseline were more likely to report inhalation incidents nine years later [41]. Cross-sectional studies also found that asthmatics more often had a history of single high exposure to irritant cleaning products than healthy controls [42-44]. A population-

based study in Northern Europe documented an increased asthma risk in men with a history of accidental peak exposure to irritants [45]. A longitudinal study of the World Trade Centre disaster, including rescue and recovery workers with intense dust cloud exposure and individuals without dust exposure showed an increased risk of new-onset asthma in the follow-up period of 5-6 years, particularly in the first months after the exposure event [46]. Longitudinal workforce-based epidemiological studies have provided evidence that the development of asthma can result from multiple high-level exposures (Table 5) [10, 30-34]. Repeated high-level exposures ("gassings" or "puffs") to chlorine in metal production workers [32] and ozone or sulphur dioxide in pulp mill workers [33, 34] were shown to be associated with an increased incidence of new-onset asthma. Repeated and/or chronic lower level exposures to irritants at work are probably common but few epidemiological studies have reported associations with asthma. The most persuasive evidence for chronic IIA related to chronic moderate irritant exposure asthma is provided by the epidemiologic studies of workers exposed to cleaning agents [47]. The frequent use of bleach (hypochlorite), ammonia, and degreasing sprays has been consistently associated with asthma among workers exposed to cleaning agents [42, 44, 48], although the precise chemical exposures and the mechanisms responsible for the increased incidence of asthma have not been clarified since cleaning materials typically contain a wide variety of ingredients, some of which are respiratory irritants, while others are potential airway sensitizers (Table 6). Other occupations associated with increased risk of asthma that cannot be readily or completely explained on the basis of a clear sensitizing exposure are presented in Table 6 [47, 49-54, 55 , 56].

NOSOLOGICAL CLASSIFICATION OF IRRITANT-INDUCED ASTHMA

IIA (or "non-immunologic/non-allergic OA") is a form of OA characterized by the development of asthma (or the reactivation of quiescent asthma) caused by exposure to irritant substances at the workplace that are capable of inducing an inflammatory reaction of the airways and NSBH through non-sensitizing mechanisms. The proposed clinical classification of IIA is based on the level of available evidence that supports a causal relationship between workplace exposure to irritants and the inception of asthma on an individual basis, which is a key element for establishing a diagnosis of asthma caused by the work environment [1-5].

This causal relationship can be documented with a reasonable level of confidence for asthma resulting from a single high-level exposure to irritants (i.e., "acute-onset IIA") and such condition should be considered as "definite" IIA. Asthma that develops, often more insidiously, in subjects with a history of multiple symptomatic high-level exposures (i.e., "subacute IIA") should be regarded as "probable" IIA. Finally, the other types of asthma attributed to chronic moderate irritant exposures at work can only be considered as "possible" IIA, since the causal relationship cannot be ascertained with certainty on an individual basis. In such settings, causality can only be inferred from epidemiological studies documenting an excess risk of asthma in similar work environments. Noteworthy, the qualifiers "definite", "probable", and "possible" are intended for clinical purposes and should not be regarded as medico-legal terms.

DIAGNOSTIC ALGORITHM

In every suspected case of IIA, the presence of asthma should be substantiated by spirometry demonstrating airflow limitation with a significant bronchodilator response or NSBH to methacholine/histamine, although airflow obstruction may be less responsive to inhaled bronchodilators in acute-onset IIA than in allergic OA [57]. In the differential diagnosis, other conditions, such as vocal cord dysfunction, hyperventilation syndrome, and multiple chemical sensitivity syndrome, should be carefully considered, especially since these “asthma-mimics” may also result from inhalation accidents and exposure to irritants in the workplace [4]. In patients with sinonasal symptoms, anterior rhinoscopy and nasal endoscopy should be considered in order to evaluate changes in nasal mucosa that may result from irritant exposures. Figure 1 summarizes the proposed algorithm for diagnosing the diverse phenotypes of IIA based on the pattern of symptom onset, distinguishing between “acute” and “delayed/insidious” (i.e., preceded by a latent, asymptomatic period of exposure) onset of asthma, and on the characteristics of irritant exposure categorized into “single high-level”, “multiple high-level”, and “chronic moderate”, although the concentrations of inhaled irritants are most often not precisely quantified.

The diagnosis of acute-onset IIA can usually be established with a high level of confidence based on the retrospective documentation of a close temporal relationship between an inhalation incident and the acute onset of asthma symptoms (Table 1 and Figure 1). Notably, a number of reports described an association between upper and lower airways symptoms after accidental exposure, giving rise to the concept of “reactive upper airways dysfunction syndrome” (RUDS) [29] or “acute irritant-induced rhinitis” [6]. Some case series [24, 25] and the “World Trade Centre Asthma syndrome” [26-28] indicate that the symptoms leading to a diagnosis of asthma may be more delayed in onset up to several months after an acute highlevel exposure incident [26, 27]. The diagnosis of probable IIA requires the documentation of multiple, symptomatic high-level exposures to irritants. Such symptomatic peak exposures can be ascertained by reports to workplace first aid units, medical records of visits to general practitioners or emergency room department, but also by the occurrence of similar conditions in fellow workers. There are some clinical features that clearly distinguish acute and sub-acute IIA from allergic OA. Subjects with IIA induced by high-level exposures do not develop work-related asthma symptoms after re-exposure to a low concentration of the irritant that initiated the symptoms, since they are not “sensitized” to the offending agent. Nevertheless, the development of specific bronchial hypersensitivity (i.e., sensitizer-induced OA) has been documented in rare cases where the single accidental exposure had been to a low-molecular-weight sensitizer [58]. On the other hand, known sensitizers may induce IIA through irritant mechanisms when inhaled at very high concentrations (Table 2) [23, 59, 60]. In such instances, specific inhalation challenges with the suspected agent may be useful to distinguish IIA from sensitizer-induced OA. Noteworthy, subjects with acute-onset IIA may experience worsening of their asthma symptoms at work because their newly acquired NSBH makes them more susceptible to various irritant stimuli at work (or outside work). Finally, unlike sensitizerinduced OA, acute-onset IIA does not require a latency period of exposure – during which the subject becomes immunologically sensitized – before the occurrence of asthma. Nevertheless, a latency period without symptoms can be present when IIA occurs after multiple high-level exposures to irritants.

Distinguishing the other phenotypes of IIA attributed to repeated, “moderate” level exposures (i.e., possible IIA) from work-exacerbated asthma, or from coincidental asthma that is not work-related, or even from immunologic OA, is elusive on a clinical basis. There are no specific diagnostic tests that can determine whether an individual truly has asthma induced by an irritant exposure. In patients who report ongoing worsening of their asthma symptoms at work, an adverse role of the workplace can be documented by assessing symptoms, pulmonary function and medication use during working periods and a vacation or temporary removal from work. In these patients, specific inhalation challenges in the laboratory or workplace challenges may be used as an attempt to distinguish IIA from work-exacerbated asthma and sensitizer-induced OA, although challenge tests with irritant substances are still poorly standardized [61].

PATHOGENESIS

There is no consensus definition of the terms “irritant” and “irritation” in the context of inhalation injury [21]. According to the USA Occupational Safety and Health Administration (OSHA), “irritants are non-corrosive substances that cause a temporary inflammation on direct contact with the skin, eyes, nose or respiratory system by a chemical action at the point of contact” [62]. However, if the irritant exposure is of sufficient intensity and/or duration, the inflammatory and remodeling processes in the airways tend to become chronic. Inhaled irritants provoke an inflammatory response with injury to the epithelial and other residential cells of the lungs. The inflammation occurs at concentrations far below those needed to cause tissue destruction, and response thresholds may vary from one person to another. Several factors may influence the pulmonary responses to irritants, such as the intensity of exposure, physical properties, such as the vapor pressure and solubility, and the chemical reactivity [21]. Although many irritants are odorous and pungent, it is worth remarking that odour is not related to toxicity. The resulting biological effect will depend on the deposition of the irritant in the upper and/or lower airways. Water soluble irritants and particles of aerodynamic diameter larger than 5 □m are predominantly deposited in the upper respiratory tract and proximal airways. Water insoluble agents and particles of 0.5-5 □m can reach the distal airways and alveoli, often without causing much sensory irritation. The potency of airborne sensory irritants can be quantified through a computerized, reproducible test based on the changes in respiratory pattern induced by increasing concentrations of chemical irritants in unanaesthetized mice [63]. Occupational exposure limits (OELs) may be set at 0.03 x RD_{50}, with RD_{50} being the concentration inducing a 50% decrease in respiratory frequency. In mice, an effect on the upper respiratory tract is quantitated by measuring a decrease in respiratory frequency (caused by a decrease in expiratory airflows at the midpoint of tidal volume), and an effect at the alveolar level is characterized by an increase in the length of a pause induced at the end of expiration. The ultimate pathogenic mechanisms of IIA remain largely speculative. Although the actions of an irritant are considered to be nonspecific [21], activation and recruitment of inflammatory and immunocompetent cells are usually observed in IIA. Inhalation of irritant compounds can induce bronchial epithelial damage, resulting in proinflammatory responses, neurogenic inflammation due to exposed nerve endings, increased lung permeability, and remodeling of the airway epithelium [64]. These effects are likely to be due to the stimulation of sensory nerves, epithelial cells and

cells of the innate immune system. Upon tissue injury, alarmins are rapidly secreted by stimulated epithelial cells and leukocytes as well as necrotic cells.
Once released, these multifunctional molecules promote the activation of innate immune cells and recruitment and activation of antigen-presenting cells engaged in tissue repair and host defense through pattern recognition receptors such as the Toll-like receptors, which recognize damage-associated molecular patterns and pathogen-associated molecular patterns. Alarmins are potent mediators of inflammation which are thought to be a critical link between the innate and adaptive arms of the immune response [65], which may explain the recruitment and activation of inflammatory cells in the airways that are typically involved in asthma pathogenesis. Chemical irritants can also directly activate sensory nerves either by stimulation of solitary chemosensory cells or by directly stimulating chemoreceptors, most importantly transient receptor potential (TRP) channels, expressed at the free nerve endings [66]. Upon activation of the sensory nerves, tachykinin neuropeptides, such as substance P, neurokinin A, and calcitonin-gene-related peptide are released locally. These neuropeptides activate their receptors located on respiratory epithelial cells and immune cells, triggering an airway neurogenic inflammation, which is characterized by plasma protein extravasation, vasodilatation, bronchoconstriction and increased mucus secretion. In addition, irritant chemicals can also activate TRP channels expressed on non-neuronal cells, including epithelial cells and inflammatory cells, thereby promoting local inflammation. TRPV1 and TRPA1 are the most commonly expressed TRP channels in the airways. The TRPV1 channel responds to capsaicin, but also to extreme increases in temperature, hydrogen concentrations and lipoxygenase products of arachidonic acid, whereas TRPA1 is activated by cinnamaldehyde, allicin and allyl isothiocyanate. TRPA1 is also activated by environmental irritants such as acrolein, tear gas, vehicle exhaust, nicotine, ozone, hydrogen peroxide and hypochlorite, defining TRPA1 as a major irritant detector. TRP channels can also be activated by local changes in osmolarity and temperature and regulated by cellular redox status. There is scant information available on pathologic changes in IIA. Bronchial biopsies in subjects with acute-onset IIA have revealed marked epithelial desquamation, inflammatory changes with predominance of lymphocytes, airway remodeling, and collagen deposition in the bronchial wall [57, 67]. Similar changes have been described in animal models [68]. Interestingly, a murine model of exposure to chlorine demonstrated acute and transient neutrophilic inflammation in lung tissue and airways and an increase in pro-inflammatory cytokines, while NSBH to methacholine persisted for at least 28 days [69]. Two human studies provided information on the long-term outcome of airway inflammation and remodeling in a large series of subjects with acute-onset IIA [67, 70]. Both showed inflammatory and remodeling profiles that did not differ from what is seen in allergic OA after removal from exposure, with an increase of eosinophils in some patients or neutrophils in others. However, the basement membrane thickness (subepithelial fibrosis) demonstrated a significant increase in patients with IIA compared to healthy subjects and subjects with nonirritant induced asthma. Altogether, the pathologic changes observed during the acute phase resemble a toxic mechanism, although the long-term phase is similar to allergic OA.

NATURAL HISTORY AND OUTCOME

The environmental and host factors that determine the initiation, persistence, or resolution of IIA remain largely unknown. Whereas in many reports of IIA there is a lack of precise information about the concentration and duration of exposure to the irritants, there is some evidence that these parameters may have a substantial impact on the development of IIA and persistent respiratory functional abnormalities. A dose-response relationship between the level of exposure assessed qualitatively by industrial hygienists and the prevalence of NSBH has been documented in subjects who had been exposed to a spill of acetic acid [24].

In a follow-up survey of pulp mill workers exposed to high levels of chlorine, the severity of gassing incidents, as evidenced by hospital emergency room visits, was a more significant risk factor for the persistence of NSBH than was the number of incidents [31]. Available information indicates that the development of acute and sub-acute IIA is not associated with smoking and atopy [24, 31]. In the study carried out in the World Trade Centre rescue and cleaning operations, the main risk factors reported for the development of a respiratory disease were the presence on the site during the first 48 hours and the duration of exposure during rescue and cleaning [71]. Smoking was a predisposing or additive risk factor while atopy was identified as a risk factor for upper but not for lower airway disease in World Trade Centre workers [72].

Few follow-up studies of patients with IIA are available. Among 51 pulp mill workers who had experienced shortness of breath for more than one month after a chlorine gassing episode, a follow-up assessment 18 to 24 months after the inhalation incident documented the presence of significant NSBH in 57% of them and airway obstruction in 31% [31].

Assessment of 19 out of the 29 workers with NSBH 12 months later revealed that six (32%) of them showed a significant improvement in NSBH, including five subjects for whom the level of responsiveness to methacholine was no longer in the asthmatic range [73]. These data indicate that NSBH can improve over several years after an acute symptomatic inhalation accident. Malo and co-workers [74] investigated the long-term outcome of acuteonset IIA in 35 subjects reassessed after a mean interval of 14 years (range, 4-24 years). At the time of follow-up, all subjects reported respiratory symptoms and 68% were treated with inhaled corticosteroids. NSBH persisted in about three quarters of the subjects, although it was improved in 39%. Airway obstruction was not significantly improved; the mean FEV_1 was 74.5% of predicted value at baseline and 69.5% at follow-up. Only 17% of subjects had normal airway calibre and NSBH at follow-up. Sputum eosinophil count was >2% in 22% of the subjects. The clinical and functional outcome of acute-onset IIA seems to be remarkably similar to what has been described in subjects with allergic OA after cessation of exposure to the causative sensitizing agent.

PREVENTION

Prevention of IIA can be considered under primary, secondary and tertiary preventive measures [75]. Primary prevention involves prevention of disease development. For IIA this requires measures that prevent exposure of workers to the levels of irritant exposures that can cause asthma. Such measures include elimination of airborne irritant products where possible, and where this is not possible, control of exposures to safe levels by occupational hygiene measures such as containment,

adequate ventilation, and, as the last option, use of respiratory protective equipment. Exposure level monitoring with alarm systems where feasible may also be appropriate in some settings when levels of potential respiratory irritants may exceed recommended levels. Educational programs for workers to ensure understanding of the potential exposures at work is important, i.e., safe handling of chemicals, how to avoid mixing chemicals inappropriately, the effective use of personal protective equipment and measures to take in the event of an accident at work that may produce airborne irritant exposures. Vocational guidance and pre-placement screening for subjects with severe asthma to avoid jobs with potentially high irritant exposure seem plausible, but the effect has not been documented. The secondary prevention measure of medical surveillance of workers does not have relevance for the occasional acute accidental exposures that generally have been associated with acute-onset IIA but theoretically might have a role to detect sub-acute and chronic IIA, although to-date this has not been evaluated. Tertiary prevention involves medical management of asthma to minimize impairment and also includes workers' compensation programs.

MANAGEMENT

Published data on the management of IIA are scarce, mainly related to case reports of acute-onset IIA. Workers who have had a high-level irritant exposure may require emergency treatment according to clinical practice guidelines [4]. They should be assessed as early as possible to determine the presence of airflow limitation or NSBH. Based on animal studies and few case reports [76, 77], it seems that treatment with systemic and/or inhaled steroids after the accident is beneficial, but the duration and dose of this treatment are still uncertain.

Unless their asthma is severe, patients with IIA who are not sensitized to workplace agents can often continue to work in the same environment with appropriate asthma management and measures to prevent a further unintentional high-level exposure to irritants [78]. Those who return to the same work environment, ideally with reduced exposure level, should receive education regarding the effects of irritant exposures in asthma and have regular medical assessment, including measurements of NSBH. If they develop uncontrolled asthma at work, they may require complete removal from the workplace. The management of IIA may be further complicated by associated disorders, such as chronic rhinitis, perceived intolerance to multiple chemicals, and post-traumatic stress disorder which can result from accidental exposure to irritant substances at work [46, 74, 79].

When applicable, compensation of IIA should be based on the same principles as those applied for other types of OA, and take into account the functional loss, the degree of NSBH, the medication need, as well as any other complications (including psychological support, as necessary).

CONCLUSION & RESEARCH NEEDS

Identifying the characteristics, mechanisms and determinants of possible IIA related to chronic exposure to irritant compounds requires further investigation in order to improve the diagnosis and initiate efficient prevention measures. Future studies, preferably in large populations, need to prioritize the assessment of exposure characteristics and the identification of host factors that impact the initiation, persistence, or resolution of the various phenotypes of IIA. In this respect, it would

be relevant to identify possible predictive biomarkers for the development and outcome of IIA. There is a need to develop and validate objective tests in order to improve the diagnosis of IIA. Prospective studies aimed at improving our knowledge on the effects of treatment and environmental factors on the outcome of IIA are required in order to improve the management of this potentially frequent work-related disease.

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TABLES AND FIGURES

Table 1. Diagnostic criteria for acute-onset irritant-induced asthma*

1.	Absence of preexisting asthma symptomatology
2.	Onset of asthma symptoms after a single specific inhalational exposure or accident
3.	Exposure to an irritant vapor, gas, fume, or smoke in very high concentration
4.	Onset of asthma symptoms within minutes to hours and less than 24 h after the exposure
5.	Presence of airflow limitation with a significant bronchodilator response or non-specific bronchial hyperresponsiveness to histamine/methacholine.
6.	Exclusion of other pulmonary disorders that can explain the symptoms or simulate asthma

* Adapted from Brooks and co-workers [9, 21] and the American College of Chest Physicians guidelines [4].

Table 2. Examples of exposures causing acute-onset irritant-induced asthma.

Exposure	Examples
Gases	Chlorine (eg released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia) sulfur dioxide, nitrogen oxides, dimethyl sulfate
Acids	Acetic, hydrochloric, hydrofluoric, and hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocides	Formalin, ethylene oxide, fumigating agents, insecticides (sodium methyldithiocarbamate, dichlorvos)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC) (thermal degradation products of freons), orthochlorobenzylidene malonitrile (tear gas), uranium hexafluoride, hydrogen and carbonyl fluoride
Solvents	Perchloroethylene
Fumes	Diesel exhaust, paint fumes, urea fumes, fire smoke, fumes of iodine and aluminium iodide, diethylaminoethanol (corrosion inhibitor)
Sprays	Various paints (not specified), floor sealant (aromatic hydrocarbons)
Dusts	World Trade Centre alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride

Table 3. Characteristics of published cases of "non-acute" irritant-induced asthma

Label (reference)	No. of subjects	Characteristics & duration of exposure	Causal agents	Pattern of asthma symptoms	Preexisting asthma /atopy	Evidence of a causal relationship
Low-dose IA Kipen, *1994* [11]	10	Daily (9 subjects); 2 mo-7 yr	Acid fumes (n=4), cutting oil, cleaning agents, perfumes, new carpet, bisulfite, chemistry laboratory	WRAS (+ work-related rhinitis in 8 subjects)	No; clinical atopy (n=4)	Adult-onset asthma, absence of exposure to known sensitizers; multiple triggers of asthma symptoms, "significantly" lower PEF values when exposed than on control days and "significant" decline in across shift spirometry in the 2 subjects still exposed
Not-so-sudden IA Brooks *1998* [12]	25	Repeated (>24 h), "moderate" level; days to months (exclusion if >16 wk)	SO2 and pesticide spraying, chlorine gas and ammonia, bleach, caustic soda; solvents and paints, etc *	NA	Yes (remission for >1 yr in 16 subjects); atopy (n=22)	Adult-onset asthma or previously quiescent asthma; absence of exposure to a known sensitizer
IIA Quirce *2000* [13]	2	Daily for 2 and 7 yr	Heated ammonia and concentrated alkaline detergent, degreasing compound	WRAS	No; atopy (n=1)	Adult-onset asthma and daily exposure to irritants products; improvement in NSBH with inhaled steroids and persistent exposure in 1 subject, resolution of NSBH after removal from exposure in 1 subject
IIA Steiner *2008* [14]	1	Daily exposure for ~3 yr; possible acute exposure before onset of symptoms	Metabisulfite (trawlerman)	WRAS	No; non-atopic	Adult-onset asthma; no evidence of sensitization to occupational agent; positive SIC with metabisulfite
IIA Adewole *2009* [15]	3	Daily for 1.5 and 5 yr; twice weekly for 15 yr	Diesel exhaust (bus garages)	WRAS	No; atopy (n=2);	Adult-onset asthma and PEF monitoring consistent with OA
IIA with latency Burge *2012* [16]	1	Daily exposure for 12 yr	Sand and lime (bricklaying without cement)	WRAS	No; atopic	PEF monitoring consistent with OA and positive SIC with sand/lime (associated with an increase in NSBH)

Legend: IIA, irritant-induced asthma; NA, data not available; NSBH, non-specific bronchial hyperresponsiveness; PEF, peak expiratory flow; SIC, specific inhalation challenge; WRAS, work-related asthma symptoms

* Causal agents are provided for "not-so-sudden onset" asthma are not detailed.

Table 4. Epidemiological studies on irritant-induced asthma related to a single high-level exposure

Reference/ country	Study design/country	Subjects (n): exposed/controls	Agents	Measure of asthma frequency	Exposed vs. non-exposed workers: OR (95% CI) unless otherwise stated
Kogevinas, 2007 [40].	Population-based longitudinal cohort study; 13 countries	Subjects with (323) vs. without (5,977) acute inhalation accident among individuals without asthma at baseline	Various inhalation accident (e.g., fires, mixing cleaning products, chemical spills)	New-onset asthma:	Acute inhalation (3.1%) vs. no acute inhalation (1.9%): RR, 1.6 (0.8-3.1)
Medina-Ramón, 2005 [42]	Population-based nested case-control study; Spain	Domestic cleaning women with (24) vs. without (152) asthma Sx	Bleach; acute inhalation (mainly due to mixing of bleach with other cleaning agents)	Asthma Sx = cases	Acute inhalation in 78% of cases vs. 51% of controls: 3.8 (1.0-14)
Delclos, 2007 [43]	Workforce-based cross-sectional study; USA	Physicians (741), nurses (941), occupational therapists (968), respiratory therapists (879)	Chemical spill at work (163 with vs 2,575 without)	Adult-onset asthma after starting work NSBH-related Sx	1.2 (0.5-2.9) 2 (1.3-3.2)
Brackbill, 2009 [46]	Longitudinal cohort study; USA	Rescue and recovery workers with intense dust cloud exposure from WTC disaster (13,770) vs. without dust exposure (24,350)	Intense dust cloud exposure on September 11, 2001	Self-reported asthma diagnosis	Intense dust cloud exposure (19.1%) vs. no dust cloud exposure (9.6%): 1.5 (1.4-1.7)
Vizcaya, 2011 [44]	Workforce-based cross-sectional study; Spain	Cleaning workers (761)	Acute inhalation due to mixing cleaning products (41 with vs. 614 without)	Recent wheeze when not having a cold	2.3 (1.0-5.5)
Lillienberg, 2013 [45]	Population-based longitudinal cohort study, 5 Northern	13,284 subjects	Accidental peak exposure to irritants based on a job-exposure matrix	New-onset adult asthma, physician-diagnosed	HR, 2.4 (1.3–4.7)
	European countries				

Legend: ; CI, confidence interval; HR, hazard ratio; NSBH, non-specific bronchial hyperresponsiveness; OR, odds ratio; RR, Relative Risk; Sx, symptoms; WTC, World Trade Centre.

Table 5. Epidemiological studies on irritant-induced asthma related to multiple high-level exposures

Reference/ country	Study design/country	Subjects (n): exposed/controls	Agents	Measure of asthma frequency	Exposed vs. non-exposed workers: OR (95% CI) unless otherwise stated
Medina-Ramón, 2005 [42]	Population-based nested case-control study; Spain	Domestic cleaning women with (24) vs. without (152) asthma Sx	Bleach; acute inhalation (mainly due to mixing of bleach with other cleaning agents)	Asthma Sx = cases	Frequent use of bleach in 50% of cases vs. 28% of controls: 12 (2.3-67)
Gautrin, 1999 [32]	Workforce-based longitudinal study (2 yrs); Quebec, Canada	Workers in a metal production plant (211)	Chlorine gassing reported to first aid unit	Significant increase in NSBH	5.9 (1.1-32.3).
[illegible]n, 2004 [33]	Workforce-based longitudinal study; Sweden	Bleachery workers (228) from pulp mills vs. unexposed workers (63)	Ozone peak exposures (symptomatic gassings)	Adult-onset asthma	No exposure: 3%; medium exposure: 11%; high exposure (≥4 gassings): 18% (P=0.005)
Andersson, 2006 [34]	Workforce-based retrospective cohort study; Sweden	Sulphite mill workers exposed to SO_2 (674) vs. non-exposed workers (849)	SO_2 (gassings)	Incidence of adult-onset asthma	Workers with any gassing (6.2/1,000 p-yrs) vs. no gassing (1.9/1,000 p-yrs): HR, 4.0 (2.1-7.7)

Legend: ; CI, confidence interval; HR: hazard ratio; NSBH, non-specific bronchial hyperresponsiveness; OR, odds ratio; Sx, symptoms.

Table 6. Examples of work exposures involved in possible irritant-induced asthma

High-risk occupation	Irritants	Irritants with a sensitizing potential	References (non-exhaustive) *
Cleaners	Bleach, ammonia, cleaning/degreasing sprays	Disinfectants (glutaraldehyde, QACs, chloramine-T, isothiazolinone), ethanolamines, enzymes, surfactants	[47]
Aluminium smelting	Fluorides, SO_2	Aluminium	[49]
Swine and dairy production	Aerosols from endotoxins & organic dusts, manure gases	QACs, animal allergens	[50]
Dark-room environment	SO_2, acetic acid	Glutaraldehyde, formaldehyde	[51]
Sulfurization	SO_2	None identified	[52]
Welding	Nitrogen oxides, fluorides, ozone	Chromium, nickel	[53]
Pesticides	Organophosphates, methylcarbamates, …	Pyrethroids, phytophagous and predatory mites	[54]
Wood industry	Wood dust	Wood dust (e.g. plicatic acid)	[55 , 56]

Legend: QACs, quaternary ammonium compounds.

* References (preferably systematic reviews) supporting an increased risk of asthma related to chronic irritant exposures at work.

Figure 1

Proposed diagnostic algorithm for identifying the various clinical phenotypes of irritant-related asthma.

IIA, irritant-induced asthma; RADS, reactive airways dysfunction syndrome.

* Onset of asthma symptoms often occurs after one more severe high-level exposure incident [10, 30].

** There is some evidence that asthma may develop within days to weeks after an acute high-level exposure incident [25-28].