Curr Allergy Asthma Rep (2014) 14:406
DOI 10.1007/s11882-013-0406-4

OCCUPATIONAL ALLERGIES (JA POOLE, SECTION EDITOR)

Irritant-Induced Asthma in the Workplace

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Published online: 17 December 2013

Abstract Irritant-induced asthma in the workplace has been the focus of several articles in the past few years, and reviewed here. A clinical case definition is most readily associated with a single acute/accidental exposure to a presumed high concentration of an agent or agents expected to be irritant to the airways, as was initially reported with the subgroup Reactive Airways Dysfunction Syndrome (RADS). When most but not all criteria for RADS are met, then a diagnosis of irritant-induced asthma may also be considered to be "more probable than not". However, in addition, there is evolving understanding from epidemiological studies that chronic exposures may be associated with an increased risk of developing asthma. Despite this recognition, the mechanisms and clinical case definitions of work-related asthma that might be caused by chronic exposures to irritants (vs. new-onset asthma that begins coincidentally to work exposures), remain unclear at present.

Keywords Asthma · Work-related asthma · Irritant-induced asthma · Occupational · Workplace · Causes · Mechanisms · Animal models · Management

Introduction

Work-related irritant-induced asthma represents a sub-group of occupational asthma, i.e., asthma that is caused by work exposure and is not due to stimuli outside of the workplace [1].

This article is part of the Topical Collection on *Occupational Allergies*

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The present article reviews recent literature published on respiratory irritants and work-related asthma, especially publications from the past 3 years. During that time, there has been greater appreciation that there is likely to be a broader spectrum of workplace exposures to irritant agents that can induce asthma than initially described, ranging from a single massive exposure incident to more chronic exposures without clear identification of unusually high concentrations. This article does not contain any data from unpublished studies with human or animal subjects.

Definitions

The term irritant-induced asthma has been used to describe asthma that has been caused by exposure to one or more agents that can act as potential respiratory irritants when inhaled [2]. Commonly, this has occurred during work, as a subset of occupational asthma, but it can also occur in non-occupational indoor or outdoor environments and domestic settings. Use of this descriptive term implies that asthma has not been caused by an antibody-associated mechanism, although in occasional circumstances, exposures that have caused irritant-induced asthma have also resulted in specific sensitization, e.g., very high accidental exposures to diisocyanates or perchlorethylene [3].

The best-defined subset of irritant-induced asthma was initially described in 1985 by Brooks [4], using the term Reactive Airways Dysfunction Syndrome (RADS). The very strict criteria specified for this diagnosis included (1) the exclusion of preceding airway disease, (2) onset of asthma-like symptoms within 24 h after an evident single, very high exposure (usually accidental), to a vapor, fume, or gas that would be expected to be a respiratory irritant, (3) persistence of symptoms for at least 3 months, and (4) objective changes of asthma on spirometry and/or documentation of airway hyperresponsiveness, e.g., by methacholine challenge. Patients who appeared to have a similar new-onset of asthma related to irritant exposure(s) but did not meet all of these

stringent criteria, could not be termed RADS, but subsequently the term "irritant-induced asthma" (IIA) has been used [5] to include both RADS and those with incomplete criteria for RADS, but in whom it was nevertheless considered likely that irritant exposure(s) had caused asthma. The criteria included under the term "irritant-induced asthma" have varied in different publications and cases/case series. Some have included exposure to dust(s), such as following the World Trade Center collapse [6, 7]; some have included more than a single exposure [5]; and/or onset of symptoms up to a few days or weeks following the exposure [7, 8]; and/or duration of symptoms for less than 3 months [9] (but usually for several weeks). However, the certainty of the association between one or more irritant exposures and onset of asthma in an individual becomes progressively less certain with greater modification of the initial RADS criteria [2].

It has also been suggested that the exposures associated with IIA might be extended to prolonged or multiple exposures that may not be considered accidental or unusual. The latter was initially suggested in small case series in which workers had developed asthma coincident with prolonged exposures that are common in similar environments, such as newly installed carpeting or second-hand smoke [10, 11]. In such individual cases it would be difficult to distinguish causation from coincidental onset of asthma. However, the possibility of chronic, moderate or low-level exposures causing asthma has been increasingly suggested from epidemiologic studies that have reported an increased prevalence of new-onset asthma in working populations expected to have frequent exposures to inhaled irritants under usual working conditions, e.g., domestic and industrial cleaning workers [12], and health care workers who are exposed directly or indirectly to sprayed sanitizers and deodorizers [13]. Although such workers may develop occupational asthma from specific sensitization to a chemical or protein in these workplaces (e.g., to quaternary ammonium compounds in cleaning products or natural rubber latex in gloves), specific sensitization has appeared unlikely to explain much of the reported asthma incidence [14], In addition, however, as a further complicating factor when there is exposure to a "mixed" environment of one or more sensitizing agents as well as one or more potential irritant agents, there may be some combined effects: non-allergens in the environment such as endotoxin might stimulate an innate immunologic response but also potentiate immunologic sensitization with concurrent exposures, e.g., to animal allergens and/or magnify responses to irritant dusts (as in farming barns [15] in which asthma is more common than expected but often is not associated with a demonstrable allergic response) (Table 1).

Baur et al [16••] in a recent review, categorized IIA into: (1) RADS, (with extremely high exposures, greater than the

Table 1 Range of potential irritant-induced asthma in the workplace

Initial criteria for Reactive Airways Dysfunction Syndrome [4]	Modified criteria that may be included for (presumed) High-exposure Irritant-induced asthma [5, 7, 24]	Suggested chronic/low-level exposures that may cause irritant-induced asthma [12–15, 16••, 29•, 30, 31, 33]
A single high-level exposure	One *or more* high level exposures	Chronic exposures with *no clearly identified high exposure*
Onset of symptoms within 24 h of exposure	Onset of symptoms *within a few days* of the unusual high exposure (up to months in WTC responders [7])	Onset of symptoms *during a working period*
Gas, fume or vapor that is expected to be a respiratory irritant	Gas, fume vapor *or* dust [7], with exposures expected to be at levels causing respiratory irritation	Gas, fumes, vapors *or dusts* that potentially can be irritant
Asthma-like symptoms severe enough to lead to acute medical attention within 24 h	Medical *assessment may be at a later time*	Medical *assessment may be at a later time*
Asthma-like symptoms that persist for at least 3 months	Asthma-like symptoms that *may resolve before 3 months* (but usually last several weeks)	*Unclear criteria* for duration
Objective evidence of asthma from bronchodilator response or test of airway hyperresponsiveness	Objective evidence of asthma from bronchodilator response or test of airway hyperresponsiveness	Objective evidence of asthma from bronchodilator response or test of airway hyperresponsiveness for a clinical diagnosis [16••], but this diagnostic term has been used in *some epidemiologic studies based on history alone*
Exclusion of previous respiratory disease	*May include those with previous allergic rhinitis*, *smoking history or childhood asthma*	*Often unclear* as to whether there was previous lung disease in epidemiologic studies
Most definitive form of IIA	Less definitive than RADS but may meet the standard of "most probable" when there are few modifications to the RADS criteria [2]	This category has most support from epidemiologic studies showing increased prevalence of new-onset asthma in workers chronically exposed to irritants such as cleaning products

occupational exposure limit (OEL), for ≤1 day; (2) not-so-sudden onset of IIA, with moderate exposures around the level of the OEL with exposures for more than 1 day but less than 4 months; and (3) low-dose IIA with exposure levels below the OEL for greater than 4 months. He has similarly proposed the following 3 conditions for considering a diagnosis of IIA:

a) The criteria originally used to define RADS [4], or
b) chronic or repeated exposures to moderate (in the TLV ranges) concentrations of an irritant agent, within permissible exposure levels and the development of asthma with a latency period, but without evidence of an IgE-mediated mechanism or
c) new-onset asthma in a highly susceptible subject (e.g., with pre-existing NSBHR) associated with exposure to an identified irritant agent even at concentrations within permissible levels.

The first two of these subsets likely provide a reasonably clear case definition for individual diagnosis and for reasons of appropriate workers' compensation. However, the third of these is more difficult to determine on an individual case basis, and to distinguish from coincidental onset of asthma. This may therefore be more relevant for public health and preventive considerations until better diagnostic tests are developed to provide a clearer case definition in this scenario. Difficulties without a clear diagnosis are discussed in a recent report of two cases [17]. Potential differential diagnoses, in addition to the coincidental onset of asthma, include conditions that may mimic asthma, including upper airway syndromes [18] and mass psychogenic illness [19].

Causes of Irritant-Induced Asthma in the Work Environment

There are multiple reported agents acutely associated with IIA that have been assumed to cause asthma by an inflammatory response resulting from one or more high-level exposures to agents that are also irritating to the airways when inhaled in relatively low concentrations. An older review by Alberts [20] listed 113 cases of IIA, and associated exposures, reported up to 1994. These included chlorine, spray paint, acids, ammonia, calcium oxide, smoke, hydrazine, uranium hexafluoride, perchlorethylene, and isocyanates. Other than their irritating properties and ability to reach the lower airways when inhaled at high concentration, there is little else that appears to be in common with these exposure agents.

More recently, Baur and colleagues [16••] have performed a systematic review of the literature up to 2012, that identifies causes of occupational irritant-induced asthma, using their definitions as described above. In this review, they also included causes of occupational COPD, but only 20 of the 474 reviewed publications were of occupational COPD and the remaining majority related to irritant-induced asthma. Baur has also published a review of both allergens and irritants causing occupational asthma [21•]. They identified 46 different agents reported to have caused IIA, associated with apparently high concentration exposures (mostly without measured concentrations but linked with an accident or unusual event) and without a latency period, with the highest prevalence after exposure reported to acids or tear gas. Almost half of their total reviewed publications (228 of 474) were case reports. The most prevalent exposure was from the World Trade Centre collapse of 2001 that included extremely high levels of inhaled alkaline calcium oxide dust, but which often did not cause asthma manifestations for weeks after exposure [7]. Other causes included in 10 or more publications comprised isocyanates, cleaning agents, chlorine, metam sodium, ammonia, and diesel exhaust. Agents that were identified relatively commonly included acids, solvents, sulfur dioxide, and dinitrogen tetraoxide. Other irritant agents have been associated with fewer reports. Overall, they identified 71 different irritant exposures with some evidence to support causation of asthma. The authors note that, from their review, most agents appeared to elicit asthma after prolonged exposure, and, rarely after a single exposure. However, in their review, they do not subdivide their findings according to single and multiple exposures, and most of their results do not separate outcomes according to asthma or COPD. Only 15 studies of irritant-induced asthma or COPD were graded as well-conducted analytic studies, or as case-control or cohort studies, and the remainder were of a lower rated level. Overall, 30 studies showed evidence of a dose–response relationship (for asthma or COPD). Among those agents considered by these authors to have moderate evidence as causing IIA (graded two stars by the Royal College of General Practitioners three star system), [21•] were chlorine, cement, environmental tobacco smoke, welding fumes, construction dusts, farming barn dusts, swine confinement facilities, and World Trade Center exposure. While these agents/exposures are likely to have acted as inhaled irritants, some have also occasionally been reported to cause occupational asthma by sensitization, such as metals in welding fumes and animal allergens in barns. However, other agents included as causes of irritant-induced asthma can also commonly act as sensitizers (such as grain, diisocyanates, trimellitic anhydride, and platinum salts). For individual cases, the mechanisms may be clarified from the exposure history, immunologic tests, and, where appropriate, by specific inhalation challenges with low, non-irritant exposure concentrations.

Mechanisms, Animal Models of IIA, and Effects of Chlorine Exposure

Mechanisms of irritant-induced asthma remain poorly understood. The initial report of RADS [4] described

epithelial cell damage and bronchial wall inflammatory changes with infiltration of lymphocytes and plasma cells. Postulated mechanisms have included inflammatory effects mediated by sensory neuropeptides such as Substance P and Neurokinin A [22, 23]. Oxidative stress may result in interleukin production such as interleukin-8 and chemokines such as MCP-1 that lead to neutrophilic inflammatory changes. Irritant exposures can activate transient receptor potential (TRP) receptors, vanilloid-1 ($TRPV_1$), and cation channel subfamily A, member 1 ($TRPA_1$) that can induce cough and may contribute to the pathophysiologic changes [24]. Chlorine gas effects both in humans and in mice models have recently been reviewed [25]. Jonasson and colleagues [26••], developed a mouse model of RADS with a single 15-min exposure to chlorine 50 or 200 ppm. The acute inflammatory response with macrophages and neutrophils resolved by 48 h, but airway hyperresponsiveness persisted for at least 28 days, suggesting that this may be a good model for further mechanistic and intervention studies. An earlier study by McGovern [27] suggested that intra-peritoneal dimethylthiourea 1 h pre- or post-exposure to chlorine gas protected against IIA in mice. Older studies suggested that corticosteroids attenuated the neutrophilic inflammatory response in rats to chlorine [28].

There have been very limited human studies of mechanisms of IIA. The range of asthmatic airway responses to irritant gases such as chlorine, sulfur dioxide, or ozone is illustrated by three recent publications. Specific challenges with chlorine 0.4 ppm, within the allowable exposure limit, have been reported by Sastre and colleagues among 13 cleaners with work-related asthma-like symptoms as well as 3 control asthmatics and 3 normal subjects [29•]. Chlorine exposure was associated with a greater fall in FEV1 compared with placebo challenge: two subjects had isolated late asthmatic responses and one had a dual asthmatic response. One subject had a significant increase in airway responsiveness to methacholine at 24 h post-challenge. There were no associated changes in sputum cell counts or exhaled nitric oxide. This report does suggest that a subset of exposed individuals can have asthmatic responses to chlorine even at relatively low levels, though the mechanism is unclear. Exposures to chlorinated compounds from swimming pools (chloramines and trihalomethanes) have also been suggested to induce new asthma in lifeguards [30], and increase risk of asthma among children, perhaps by increasing lung epithelial permeability [31, 32].

Higher exposures to irritants are expected in pulp mills where there can be intermittent episodes of "gassing" from ozone and other bleaching agents that have been associated with new-onset irritant-induced asthma [33]. A recent analysis [34•] of a cohort of paper mill workers indicated that over a third reported at least one gassing exposure during their work in the mill; these irritant peak exposures to chlorine/chlorine dioxide or sulphur dioxide were associated with increased work disability and resultant changes in work (hazard ratio 5.3, 95 % CI 2.7–10.5).

In an MMWR report [35], acute (presumed high) exposure to chlorine gas accidentally occurred at a poultry plant, when sodium hypochlorite was inadvertently poured into a drum containing residual acidic antimicrobial solution. Six hundred workers were evacuated, 195 sought medical care, and 152 reported being hospitalized. Five months later, 105 workers had symptoms of new-onset asthma and, at 7 months after the accident, 3 had confirmed RADS on the basis of history and methacholine response and another 3 had borderline RADS (a borderline positive methacholine response).

Management of Irritant-Induced Asthma

Following an accidental high-level irritant exposure at work, appropriate immediate management includes rapid removal/protection from exposure according to safety guidelines in the workplace (e.g., evacuation of workers and use of respiratory safety equipment by those responsible for managing the accident). A high-concentration exposure often represents a failure of safety practices, such as recently described where labeling of a container was not understood by an initial worker and then was not read by the next worker, resulting in dangerous mixing of chemicals [35]. An acute inhalation accident may require on-site intervention such as eye-wash or other measures and may require acute medical assessment and supportive management, as well as any specific measures to reverse chemical effects that are beyond the scope of this review. Acute airway responses should be assessed early and may require supplemental oxygen, bronchodilators, and corticosteroids. Although there is little objective evidence for the effectiveness for systemic corticosteroid therapy, this is often used for treatment in the hope of limiting airway inflammation.

Subsequent management also includes pharmacologic treatment of asthma as appropriate as well as control of further workplace exposures to expected irritants that may exacerbate asthma. Avoidance of high/accidental irritant exposures as far as is feasible is advised to prevent development of asthma in other workers.

Conclusions

Recent publications suggest a reconsideration of the role of irritants in causing asthma, to include not only the very high exposures previously recognized to be able to cause asthma in a subset of exposed workers, likely from acute inflammatory responses, but also more chronic, lower exposures that may

cause asthma by unclear mechanisms. Currently, however, there are no clinical diagnostic criteria that enable the attribution of new-onset-asthma to low irritant exposures at work in an individual patient, and to distinguish this from the coincidental onset of asthma.

Compliance with Ethics Guidelines

Conflict of Interest Susan M. Tarlo has had travel expenses covered/reimbursed for participation in European Academy of Allergy, Asthma and Clinical Immunology task forces.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. Any human studies by the author were performed with informed consent and research ethics approval.

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