

Occupational asthma

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SUMMARY

Work-related asthma is highly prevalent and represents a significant societal and financial burden worldwide. This State of the Art series article explores the epidemiology, clinical features, diagnosis and management of occupational asthma (OA), which comprises sensitiser-induced asthma and irritant-induced asthma (IIA). Sensitiser-induced OA is the development of asthma through sensitisation to a substance in the workplace. OA is largely underdiagnosed, and its clinical manifestations are non-specific, which makes its diagnosis challenging. Early and accurate diagnosis of OA through comprehensive testing is primordial to

avoid unwarranted removal from exposure and to allow early management of confirmed cases. Despite optimal management, up to 70% of patients with OA will have persistent asthma several years after diagnosis. IIA classically refers to the development of de novo asthma acutely following an intense exposure to an irritant agent. However, some cases of IIA following multiple high-level exposures or a chronic low-dose exposure have been reported.

KEY WORDS: occupational lung disease; irritant-induced asthma; work-related asthma; sensitiser-induced asthma

ASTHMA IS A CHRONIC INFLAMMATORY disorder of the airways that affects more than 300 million people worldwide.¹ It is thought that up to 25% of adult-onset asthma is work-related.² Work-related asthma (WRA) is a broad term referring to asthma that is worsened by the workplace. WRA encompasses the clinical entities of asthma caused by a specific agent in the workplace (i.e., occupational asthma [OA]), as well as pre-existing asthma that is worsened by exposure to non-specific stimuli at work, but not caused by it (i.e., work-exacerbated asthma [WEA]). WRA is a major public health concern due to its important financial and societal burden and its high prevalence. In this State of the Art review, we will focus on occupational asthma, both sensitiser-induced OA and irritant-induced OA, but we will not be covering WEA. The Medline, Embase and Cochrane Library databases of Systematic Reviews were searched using the terms 'occupational asthma', 'work-induced asthma', 'irritant-induced asthma' and 'reactive airways dysfunction syndrome' from 1 January 1990 to 1 March 2019. Reference lists of selected studies were also analysed to detect relevant studies.

DEFINITIONS

The American College of Chest Physicians' consensus statement on WRA defines OA as,

...de novo asthma or the recurrence of previously quiescent asthma (i.e., asthma as a child or in the distant past that has been in remission) induced by either sensitisation to a specific substance (e.g., an inhaled protein [high molecular-weight (HMW) protein of >10 kD] or a chemical [low-molecular-weight (LMW) agent]), at work, which is termed sensitiser-induced OA, or by exposure to an inhaled irritant at work, which is termed irritant-induced OA.³

OA can thus be subdivided into two types based upon its pathogenesis. Sensitiser-induced OA, also known as 'immunologic OA', 'allergic OA' or 'OA with latency period', implies that asthma is caused by immunologic-mediated sensitisation to a substance in the workplace.⁴ These sensitising agents include HMW (glyco) proteins of vegetable or animal origins, as well as LMW agents, which include chemicals, metals and wood dust (Table 1). Despite the large number of known sensitisers, 50–90% of sensitiser-induced OA cases are due to a limited number of substances (i.e., diisocyanates, flour, hairdressing products, latex, animals, metals, wood dust).^{5,6} The frequency of OA cases due to different causal agents varies between countries due to geographic differences in industrial activities and different diagnostic criteria.

Sensitisation to HMW agents and a few LMW agents (e.g., reactive dyes, platinum salts, obeche

Table 1 Common agents causing occupational asthma

Agents	Occupation/workplace
High-molecular weight agents	
Cereal, flour	
Wheat, rye, buckwheat, barley	Bakers, pastry makers, flour mills
Animals	
Rats, mice, rabbits, seafood	Laboratory workers, seafood processing
Enzymes	
Amylase, subtilisine, maxatase, pancreatin, bromelain	Bakers, detergent use/production, food and pharmaceutical industries
Latex	
Hevea tree protein	Healthcare workers, laboratory workers
Low-molecular weight agents	
Diisocyanates	
Toluene diisocyanate, hexamethylene diisocyanate, methylene diphenyl-diisocyanate	Polyurethane production, insulation, plastic industry, spray painting
Acrylates	
Cyanoacrylates, methacrylates, di- and tri-acrylates	Adhesives, dental materials, fingernail salon, printing inks, paint and coatings
Persulphate salts	
Hairdressing products (bleach)	Hairdressers
Biocides	
Formaldehyde, glutaraldehyde, quaternary ammonium compounds	Cleaners, healthcare workers
Metals	
Chromium, nickel, cobalt, platinum	Welding, metal refinery, electroplating, metal alloy production
Wood dust	
Western red cedar, iroko, obeche, oak	Sawmill workers, wood workers, carpenters, furniture and cabinet makers
Acid anhydrides	
Phthalic, trimellitic, maleic anhydrides	Epoxy workers
Amines	
Triethanolamine, ethylene diamine, isophorone diamine	Epoxy workers, photography, fingernail salon, spray paint, soldering

wood) is mediated through immunoglobulin E (IgE),⁷ while the mechanism leading to sensitisation to most LMW agents (e.g., isocyanates, aldehydes, anhydride acids, acrylates) is still unclear.⁸

By contrast, irritant-induced (occupational) asthma (IIA)—also known as ‘OA without a latency period’ or ‘non-immunological OA’—arises from exposure to an irritant agent, either after an acute inhalational accident or following repeated exposures.⁹ The most commonly described presentation is that of reactive airways dysfunction syndrome (RADS), where asthma symptoms start within 24 h of a single, massive irritant aerosol, gas, vapour or fume exposure.^{9,10} Other phenotypes of IIA are emerging, where asthma develops insidiously over time after either an acute exposure to an irritant (e.g., World Trade Centre rescue workers) or after persistent exposure to low-level exposures of irritant agents over time, such as professional cleaners; also known as ‘not so sudden IIA’ or ‘low-dose RADS’ (Figure).⁹

SENSITISER-INDUCED ASTHMA

Epidemiology

Sensitiser-induced OA is the most common form of OA, representing more than 90% of OA cases.¹¹ There is a wide variation in the reported incidence of OA, ranging from 13 to 178 new cases per million workers (Table 2). This variability is likely to be

Table 2 Estimated incidence for occupational asthma

Country	Year(s)	Estimated incidence (number of cases per one million workers)
United Kingdom		
Whole country	1992–2001	87 ¹¹⁴
West Midlands	1991–2011	35 ¹⁹
United States		
Michigan	1995	27 ¹¹⁵ (48–204)*
California	1993–1996	25 ¹¹⁶ (23–27)
Canada		
British Columbia	1991	92 ¹¹⁷
Quebec	1992–1993	42–79 ¹¹⁸
France	1996–1999	24 ¹¹⁹ (22–25)
South Africa	1997–1999	18 ¹¹¹
Australia	1997–2001	31 ¹²⁰ (27–36)
Spain	2002	57 ¹²¹ (52–62)
Belgium	2000–2002	24 ¹²² (19–29)
Belgium	1993–2002	29 ⁶ (28–31)
Finland	1989–1995	174 ¹²³
Canada (Quebec)	1989–1999	13–24 ¹²⁴
Sweden	1990–1992	80 ¹²⁵ (70–90)
Germany	1970–2005	24 ¹²⁶ (12–35)
Scandinavia (Denmark, Iceland, Norway, Estonia, Sweden)	1999–2001	Men: 182 ¹²⁷ Women: 168 [†]
United States	2006–2009	178 ¹²⁸ (113–245)
Finland	1986–1998	Men: 478 ¹²⁹ Women: 419 [†]
European Community Respiratory Health Survey	1990–1995 1998–2003	250–300 ¹²

* Indirect estimates from ‘capture-recaptures’ technique.

† Estimated from the proportion attributable risk of new-onset asthma due to occupational exposure.

explained by several factors: 1) the studies originate from a variety of countries with different health care systems and different diagnostic criteria; and 2) different types of industries bearing different risks of developing OA are described, which affect the reporting of OA cases. The design of the studies also affects the incidence reported; for example, medico-legal statistics from workers' compensation programmes may be more accurate in reporting confirmed cases of OA, but are likely to underrepresent workers not eligible for compensation programmes. In contrast, population surveys yield larger estimates of OA and reduce the risk of 'healthy-worker effect' bias from workplace studies, but are limited by the lack of objective testing to confirm OA. For example, the European Community Respiratory Health Survey II estimates a yearly incidence of OA up to 300 cases per million,¹² which is significantly higher than medico-legal statistics or physician-based notification schemes.

OA incidence also varies between industries. Cohort studies reported 0.9 cases of OA per 100 person-years (py) among workers in toluene diisocyanates (TDI) production,¹³ 1.8 per 100 py among dental apprentices exposed to latex gloves,¹⁴ and 4.1 per 100 py among workers exposed to wheat flour.¹⁵

Overall, OA incidence appears to be decreasing over time.^{6,16–18} It is unclear if this represents a true decline in OA incidence arising from effective preventive measures or if it reflects a decline in diagnosis and notifications.^{16,19}

Pathogenesis

Most HMW agents and some LMW agents (e.g., platinum salts, acid anhydrides) induce asthma through IgE-dependent mechanisms.⁷ HMW agents lead to IgE production by acting as complete antigens, while LMW agents must conjugate with host proteins (e.g., albumin, haemoglobin) to form functional haptens. The cross-linking of IgE antibodies on mast cells, basophils and macrophages gives rise to signalling cascades that lead to inflammatory cell activation, similarly to non-work-related allergic asthma. For most LMW agents, the role of IgE-related mechanisms is less clear. In wood workers exposed to Western Red Cedar, the presence of serum-specific IgE antibodies (sIgEs) to plicatic acid was similar in subjects with and without respiratory symptoms, suggesting that sIgEs may solely reflect exposure to the agent rather than a clinical disease.²⁰ Similarly, sIgE antibodies to diisocyanates are detected in up to 55% of workers with confirmed OA related to diisocyanates.^{21,22} Specific IgEs to diisocyanates seem to have a good specificity for the diagnosis of diisocyanates OA but low sensitivity.^{23,24} IgG production can be found in subjects exposed to sensitising LMW agents, although their significance is

unclear and may reflect exposure rather than disease.^{23,25,26}

Most LMW agents rely on IgE-independent immunologic pathways that are poorly understood. A murine model of asthma induced by hexamethylene diisocyanate revealed an expression of interleukin (IL) 5, IL-13 and interferon-gamma in bronchoalveolar lavage (BAL), suggesting a mix of type 2 and non-type 2 inflammations.²⁷ Myeloperoxidase, metalloproteinase 9 and IL-8 were detected in airways of patient with TDI-induced OA following bronchial challenge to TDI, suggesting neutrophilic inflammation.²⁸ Other studies suggest that LMW agents could trigger inflammatory changes through reactive oxygen species and production of autoantibodies.²⁹

Risk factors

Environmental risk factors

- 1) The level of exposure to a sensitising agent is the most recognised environmental risk factor for the development of OA. Some studies have suggested a dose-response relationship between the level of exposure and development of IgE-mediated OA,^{30,31} which may be more pronounced in an early career.³² Individual variability may affect the exposure-response relationship, as certain human leukocyte antigen (HLA) class II polymorphisms were associated with OA at low-level exposure to platinum salts.³³ Inversely, there is limited evidence that a high-level exposure to laboratory animal allergens may be protective against IgE-mediated sensitisation and allergy symptoms through a modified T2 response.⁵ Dermal exposure to LMW agents can lead to eosinophilic airway inflammation and airway hyperresponsiveness (AHR) in animals,³⁴ but no studies has examined the impact of non-respiratory exposure to agents on the development of OA in humans.
- 2) Cigarette smoking has been shown to increase IgE sensitisation to HMW and LMW agents,³⁵ but the evidence linking smoking to the development of OA is weak.⁵
- 3) Occupational exposure to vapours, dust, gas and fumes is associated with an increase prevalence of asthma, of which the proportion of OA is unknown (Table 3).³⁶

Individual risk factors

- 1) Atopy, rhinitis and previous evidence of AHR are strong risk factors for the development of OA due to HMW agents.^{37,38} Atopy increased the risk of OA up to eight-fold in bakers/pastry makers, but was not associated with an earlier onset of symptoms.³⁹ In apprentices exposed to laboratory animal, known sensitisation to pets on entry to the workplace increased the risk of OA by four-fold.³⁸

Table 3 Risk factors for sensitiser-induced occupational asthma

Risk factor	Agent
Atopy	HMW agents: flour, ^{130–132} laboratory animals, ^{32,38,39,132,133} hair products, ⁷⁶ latex ^{14,132} LMW agents: wood dust ^{134,135}
Work-related rhinitis	Mixed sensitisers, ^{136,137} laboratory animals, ^{138,139} latex, ¹⁴ diisocyanates, ¹⁴⁰ flour/ α -amylase ¹³⁰
Non-specific bronchial hyperresponsiveness	Laboratory animals ³⁸
Genetic markers/ HLA class II alleles	HMW agents: laboratory animals, ¹⁴¹ latex ¹⁴² LMW agents: diisocyanates, ^{143–151} acid anhydrides, ^{152,153} platinum salts, ³³ red cedar ¹⁵⁴
Tobacco smoking	Platinum salts, ^{155,156} laboratory animals ¹⁵⁷
Skin exposure	Diisocyanates ^{34,158}
Level of exposure	Diisocyanates, ^{13,30,31,159} wheat flour, ^{70,160,161} α -amylase, ¹⁶² laboratory animals, ^{32,132,157,163–165} detergent enzymes, ^{166,167} snow crab processing, ¹⁶⁸ latex, ^{132,169} platinum salts, ^{155,156,170} acid anhydrides ¹⁷¹

HMW = high molecular weight; LMW = low molecular weight; HLA = human leukocyte antigen.

- 2) Genetic markers, including HLA class II polymorphisms (i.e., HLA-DR and HLA-DQ alleles) and single nucleotide polymorphisms on different genes (e.g., *CTNNA3*, *MBL2*, *HERC2*) have been associated with both susceptibility to and protection against OA.⁴⁰

CLINICAL FEATURES AND DIAGNOSIS

Clinical symptoms

OA is difficult to diagnose and remains largely under-recognised. Patients may not be aware of the relationship between their occupation and their symptoms or may be reluctant to seek medical advice due to fear of professional or financial consequences.⁴¹ Physicians often fail to take an appropriate occupational history and to look for an association between workplace exposure and respiratory symptoms.^{42,43} Despite strong evidence showing that early diagnosis of OA leads to improved outcomes,⁴⁴ the diagnosis of OA is usually made 2–4 years following the onset of symptoms.⁴²

Respiratory symptoms of sensitiser-induced OA (i.e., intermittent shortness of breath, chest tightness, wheezing) are generally similar to that of non-WRA, but their severity is often modulated by the level of workplace allergen exposure. Specific features of OA will include a relationship between workplace exposure and symptoms. The latency period between the initial exposure and the beginning of the symptoms is

variable, classically between a few weeks to a few years. Rhinitis and conjunctivitis symptoms may precede OA, especially in OA due to HMW agents.⁴⁵ Patients with OA frequently report occurrence or worsening asthma symptoms at work, which resolve or improve away from work (e.g., weekends and holidays). This is usually true early in the course of the disease; as duration of the ongoing exposure and symptoms increase, patients are less likely to have a complete resolution of their symptoms with avoidance of the workplace exposure.^{46–48}

Late asthmatic reactions to the allergen, leading to symptoms worsening towards the end of the day or after working hours, and the presence of non-specific respiratory irritants or indoor allergens at home may confound the evaluation of WRA.⁴⁶

Occupational history

Relevant information pertaining to occupational history includes the patient's current and previous occupations (tasks, work environment, respiratory protective precautions), direct and indirect exposure to potential asthmagens—by examining the Material Safety Data Sheets [MSDS] of the potential agents—and associated symptoms (rhinitis, conjunctivitis, dermatitis). It is also important to clarify the patient's respiratory symptoms, nature, latency period, preceding associated symptoms (e.g., rhinitis) and temporal association with work. Asking the patient to bring pictures or a drawing the workplace's floorplan may facilitate the occupational history. Since there are over 400 known workplace sensitisers,⁴⁹ with new ones being discovered every year, the absence of an obvious sensitising agent in the workplace alone does not exclude the diagnosis of OA.

The occupational history and clinical symptoms are not sufficient to make the diagnosis of OA, as only half of the patients with a suggestive history end up being diagnosed with OA following proper testing.⁵⁰

Diagnostic tests

Once the history has been obtained, asthma needs to be objectively confirmed either through the documentation of reversible airflow obstruction (e.g., pre- and post-bronchodilator spirometry, peak flow monitoring) and/or AHR (e.g., methacholine, mannitol, or exercise bronchial provocation tests). Of note, absence of AHR following a period where the patient was not exposed to the workplace does not exclude the diagnosis of OA.⁵¹ Investigation for OA should be performed preferably while the patient is still employed, so that at-work and off-work comparisons of asthma activity can be assessed through serial peak flow monitoring and serial measures of airway responsiveness.

Measuring sIgEs or performing skin prick tests (SPTs) is helpful mainly with HMW agents, which

clearly involve IgE-dependent mechanisms. Their use is limited by the lack of standardised SPT solutions for most agents. sIgEs to diisocyanates have a high positive predictive value (PPV) for the diagnosis of OA, although the sensitivity is low (44% for OA caused by TDI).⁵² There is weak evidence for the use of SPT to platinum salts in surveillance programmes for at-risk workers.⁵³

Specific inhalation challenges (SICs) are considered the 'reference test' for OA if the diagnosis is still unclear after initial testing, although there can be false-negatives and false-positives. SICs are frequently used to confirm the diagnosis of OA by workers' compensation boards in some jurisdictions such as Spain, Italy, Finland, Belgium, Poland and the province of Quebec, Canada. The European statement on SICs emphasises that they should be performed in expert centres under close supervision and should include a control challenge and a gradual increase in exposure to the suspected agent.⁵⁴ The consensus statement defines a positive reaction as a decrease in forced expiratory volume in 1 s (FEV₁) from the baseline of $\geq 15\%$,⁵⁴ although some centres use a cut-off of 20%. The limited access and high costs may limit its usefulness for physicians practicing outside of specialised academic centres.

Non-invasive measure of airway inflammation

Sputum cell counts can help the diagnosis of OA in showing an increase in sputum eosinophils at work decreasing after a period away from work.⁵⁵ It can also help to differentiate OA from WEA where no increase of sputum eosinophils is found after exposure to the offending agent.⁵⁶

Blood eosinophil counts have a weak correlation to sputum eosinophilia. Although patients with OA to HMW agents confirmed by SIC have higher baseline serum eosinophilia (>300 cells/ μ l) than patients with confirmed OA to LMW agents,⁵⁷ the change in blood eosinophil counts failed to differentiate workers with positive and negative SICs.⁵⁸

Fractional exhaled nitric oxide (FeNO), a surrogate marker of airway inflammation, is simple, easy to obtain measurement providing immediate results. However, its results are confounded by several factors, including atopy, smoking, sinus disease and inhaled corticosteroid use. The use of FeNO in the diagnosis of OA is controversial. Cut-offs of 8.5 and 10.5 parts per billion (ppb) had sensitivities of respectively 80% and 70% for OA, making it a poor screening tool.⁵⁹ When compared to sputum eosinophil counts, a 2.2% increase in sputum eosinophilia achieved a much higher sensitivity and PPV than a 10-ppb change in FeNO.⁶⁰ A recent study suggests that an increase in FeNO of ≥ 13 ppb following SIC has a sensitivity of 50% and a specificity of 90%, although sputum eosinophil counts were not analysed, and some of their positive SIC results were doubtful.⁶¹

Adding FeNO measures and sputum cell counts to non-specific bronchial hyperreactivity (NSBHR) increases sensitivity from 87% to 94% compared to NSBHR alone.⁶²

Combination of tests

By using SIC as the 'reference test', NSBHR—defined by a concentration of methacholine causing a fall in FEV₁ $> 20\%$ (PC20) of ≤ 16 mg/ml—had a relatively high sensitivity (87–95%) and a low specificity (36–40%) for the diagnosis of OA.^{51,62} Racine et al. found that combining a ≥ 2 -fold decrease in PC20 and a $\geq 3\%$ increase in sputum eosinophil counts achieved a sensitivity of 84% and a specificity of 74% with a negative predictive value of 91% for the diagnosis of OA.⁵⁸

Prevention, outcomes and treatment

Once the diagnosis of sensitiser-induced OA is confirmed, complete avoidance of the causal agent is recommended as the optimal treatment.³ This can be achieved by changing the substance used at work to a non-sensitising agent (e.g., quaternary ammonium compounds, diisocyanates, enzyme-based detergents), but this is often not feasible. The patient may need to be relocated to a different occupation either in or outside the workplace, which can lead to a substantial socio-economic impact.⁶³ If relocation is not possible or not desired by the patient, interventions to decrease the exposure are reasonable options, although not as effective as complete removal from exposure.⁶⁴ Exposure reduction can be achieved through relocation inside the workplace, optimisation of personal protective equipment and education through training programmes.

Despite complete avoidance of exposure, asthma will persist in the majority of patients. Respiratory symptoms and AHR persist in 70% of patients even several years following removal from the source of exposure.⁴⁴ Early diagnosis through workplace medical surveillance was associated with a better prognosis compared to patients identified through the usual methods, which highlights the importance of early diagnosis and removal from exposure.⁶⁵ Other than avoidance of exposure, all patients with sensitiser-induced OA should be managed similarly to other asthma patients with regards to asthma education, avoidance of environmental triggers and appropriate pharmacotherapy according to asthma guidelines.⁶⁶ Allergen immunotherapy has been reported to be helpful in OA caused by some HMW agents in some case series, although the evidence is weak.⁶⁷ The use of biological agents such as omalizumab was found to be useful in treating OA due to LMW and HMW agents in only a small number of patients,⁶⁸ as well as in animal studies.⁶⁹

Primary prevention aims at preventing development of sensitisation to workplace agents, hence

Table 4 Prevention of sensitiser-induced OA

Primary prevention
Avoid introduction of new sensitising agents in the workplace
Use alternatives to sensitising agents
Modify chemical or physical form of the agent to decrease its sensitising potential (e.g., polymerised products, less volatile products, latex gloves with low protein and powder content)
Education programmes for workers regarding safe practices
Monitor and control exposure levels
Secondary prevention (early detection of OA)
Institute medical surveillance programmes for at-risk workers (questionnaires, spirometry, etc.)
Educate workers about risks of OA and signs/symptoms of the disease (education programmes, written information, information by healthcare provider, etc.)
Educate healthcare workers about OA
Tertiary prevention (appropriate treatment of OA)
Initiate appropriate investigations to achieve early diagnosis
Remove workers from further exposure to causal agent once diagnosis is confirmed (if possible)
Non-pharmacological and pharmacological treatment to control asthma
Assist patient with work-compensation claim (if applicable) to limit socio-economic impact of diagnosis
Monitor patient's asthma control in future work environment to ensure safe placement

OA = occupational asthma.

preventing the development of OA. Control of exposure through different methods (Table 4) is thought to decrease the risk of developing OA given the known dose-response relationship between the level of exposure to sensitising agents and the development of sensitiser-induced OA.⁷⁰ Identifying at-risk individuals before employment and excluding them from high-risk occupations based on risk factors for OA (atopy, baseline NSBHR) (Table 3) is inefficient and discriminating, as these risk factors are highly prevalent in the general population and have a poor predictive value for the development of OA.³

Secondary prevention refers to surveillance programmes (e.g., medical questionnaires, spirometry, immunological testing) allowing early detection of OA in at-risk workers exposed to workplace sensitisers, and to achieve early removal from further exposure once the diagnosis is confirmed, when possible. Such programmes were shown to lead to improved outcomes compared with OA detection through standard methods.⁶⁵

IRRITANT-INDUCED ASTHMA

Epidemiology

RADS and IIA comprise 5–18% of OA cases reported by workers' compensation boards and medical surveillance programmes across different countries.^{71,72} A limited number of studies report the impact of acute high-concentration inhalation events on the burden of asthma in workers. A large multinational European prospective health survey showed that workers who reported an acute symp-

tomatic inhalation event (e.g., exposure to a spill, fire, mixing or cleaning products) had a three-fold increased risk of new-onset asthma.¹² Similarly, cross-sectional studies of professional cleaners have shown that individuals with asthma will more often report a history of an acute inhalation accident compared to non-asthmatic controls.^{73,74} Longitudinal follow-up of fire department rescue workers who were exposed to high levels of aerosolised dust and smoke following the World Trade Center (WTC) attacks in 2001 showed that up to 25% of tested subjects developed persistent bronchial hyper-responsiveness and respiratory symptoms,⁷⁵ some of which persisted up to 12 years after the event.⁷⁶ Similarly, up to 5% of screened subjects following exposure to the derailment of a train releasing 54 metric tons of liquid chlorine in Graniteville (SC, USA) had new onset physician-diagnosed asthma 10 months after the event.⁷⁷

Cross-sectional and longitudinal studies of workers with repeated moderate-to-high level exposure to chlorine, sulphur dioxide or ozone have shown an increased risk of self-reported and physician-diagnosed asthma compared to controls.^{78–81}

'Acute IIA' (RADS) has originally been described as the occurrence of respiratory symptoms within 24 h following an identifiable acute inhalation event to an irritant compound. More recently, other phenotypes of IIA such as 'low-dose IIA' or 'chronic IIA' have been described. In those phenotypes, asthma appears insidiously after several years of chronic low-dose exposure to irritants. These types of IIA are difficult to differentiate from work-exacerbated asthma in an individual patient. However, the existence of this phenotype is supported by epidemiological studies showing that chronic and/or repeated exposure to low-dose irritants in professional cleaners and healthcare workers (e.g., chlorine bleach, ammonia products) is associated with a higher incidence of asthma compared to the general population.^{73,82–84}

Pathogenesis

Inhaled irritants usually arise from spills of a volatile substance, an emanation of combustion products or a reduction of ventilation in a confined environment.⁸⁵ Several factors can influence the airway response to irritant agent exposure, including the properties of the exposed substance (e.g., solubility, gas pressure, chemical reactivity, size of the particles), intensity of exposure, adequacy of environmental ventilation, use of personal protective equipment and the individual's susceptibility. Several agents at high-level exposures have been reported to cause IIA. In individual cases, the exact nature, content and concentration of the irritant compound is often unknown as the inhalation is often accidental and occurs without warning.⁸⁵

Mechanisms of IIA remain poorly understood.

Table 5 Phenotypes of irritant-induced asthma (adapted from Vandenplas et al., 2014)⁹

Characteristics	Definite IIA	Probable IIA	Possible IIA
Mode of exposure	Single, high-level	Multiple, moderate-high-level	Chronic, low-moderate-level
Onset of asthma	Acute*	Delayed/insidious†	Delayed/insidious
Clinical characteristics	No latency period Close temporal relationship between exposure and onset of asthma symptoms	Latency period Documentation of repeated symptomatic exposures	Latency period Epidemiological evidence of asthma in high-risk occupations
Other terminology	'Acute-onset IIA', 'RADS'	'Sub-acute IIA'	'Low dose IIA', 'not-so-sudden IIA', 'IIA with latency'

* Asthma can develop within days to weeks after a high-level exposure.

† Onset of asthma can occur after a more severe symptomatic inhalation event.

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

Irritant agents were shown to cause injury to the airway epithelium leading to airway inflammation, increased lung permeability, neurogenic injury and airway remodelling.⁹ Multiple cytokines, alarmins, transient receptor potential channels and Toll-like receptors are implicated in the recruitment of inflammatory cells in response to the irritant-induced airway injury.⁹ Independent from epithelial damage, sensory nerves can be directly affected by the irritant agent through the stimulation of neuroreceptors, followed by the release of neuropeptides such as substance P and neurokinin A.⁸⁵

Murine models of IIA in which BALs were performed show an elevated number of neutrophils^{86–88} compared to sensitiser-induced asthma, which usually reveals eosinophilic and/or lymphocytic inflammation.⁸⁹ Compared to wild-type mice, Nrf2- and CysLTR1-deficient mice have more prolonged neutrophilic inflammation and AHR, suggesting that the loss of antioxidant protective effects from the Nrf2-dependent enzymes may play a role in IIA pathogenesis.^{90,91} Bronchial biopsies in rats exposed to chlorine showed epithelial flattening with evidence of regeneration and an increase in smooth muscle mass.⁸⁶

Similar to animal studies, BAL fluid analyses show predominantly increased neutrophil counts in patients with IIA.⁹² Histopathological changes from bronchial biopsies in patients with IIA showed inflammatory and remodelling changes similar to that of non-IIA, although there was evidence of thickening of the basement membrane to a greater extent than in non-IIA.^{92–94}

Risk factors

Risk factors for IIA are still largely unknown. Indirect evidence suggests that the risk of developing acute IIA (RADS) depends on the severity of the exposure. The longitudinal follow-up of pulp-mill workers showed that workers who reported severe gassing (i.e., leading to an emergency room visit) had higher odds of developing NSBHR than workers reporting several non-severe gassings.⁹⁵ Similarly, qualitative assessment of the exposure by an industrial hygienist was associated with the development of NSBHR in

workers exposed to a spill of acetic acid.⁹⁶ In both cases, atopy and smoking were not associated with the development of IIA. Among fire department rescue workers following the WTC attacks, a high-intensity exposure (i.e., arriving on site on the morning of the attacks) was the strongest predictor of the development of asthma.⁹⁷

Diagnosis

The best defined subtype of IIA was first described by Brooks et al. in 1985 using the term reactive airways dysfunction syndrome (RADS).¹⁰ The criteria for RADS were very strict and included 1) exclusion of a previous respiratory disease; 2) the onset of asthma-like symptoms within 24 h of a clear exposure to an irritant agent (vapour, gas, fumes); 3) persistence of symptoms for at least 3 months; and 4) objective reversible airflow limitation on spirometry and/or evidence of NSBHR. Patients who developed asthma following the inhalation of irritants who did not fit the strict RADS diagnostic criteria were then termed 'irritant-induced asthma' of a different phenotype. For example, some case series^{96,98} and reports of the WTC-related asthma syndrome⁹⁷ indicated that the asthma-related symptoms may develop insidiously over weeks to months following a massive exposure.

Given the recognition of the various clinical presentations of IIA, the European Association of Allergy and Clinical Immunology has proposed new definitions for different IIA phenotypes in their position paper on IIA:⁹ 1) definite IIA relates to acute-onset IIA manifested by rapid onset of asthma within 24 h of a single very high-intensity exposure to an irritant compound (similar to the classic RADS phenotype); 2) probable IIA is the development of asthma following multiple symptomatic moderate-high-level exposures to irritants; and 3) possible IIA is a delayed development of asthma following chronic and/or repeated exposure to low-moderate levels of irritant substances (Table 5). In cases of possible IIA where the development of asthma is insidious and is not clearly linked to a very high irritant exposure, it is often difficult to distinguish IIA from coincidental onset of personal asthma.

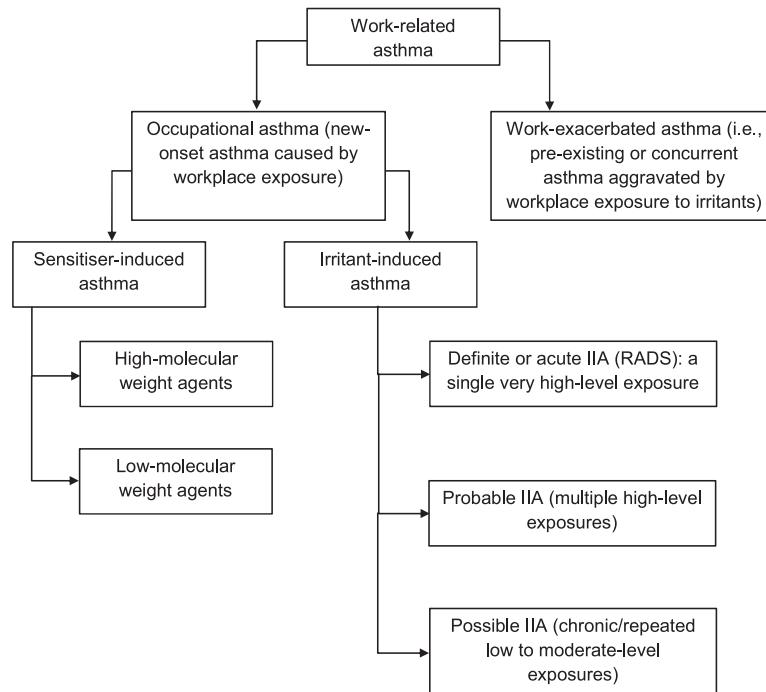


Figure Adapted from Murray and Nadel's Textbook of Respiratory Medicine.¹⁷² IIA = irritant-induced asthma; RADS = reactive airway dysfunction syndrome

In all cases, the diagnosis of asthma must be confirmed either by evidence of variable airflow obstruction on spirometry or evidence of NSBHR to methacholine or histamine. It is important to consider alternative diagnoses that can mimic asthma symptoms following exposure to respiratory irritants such as irritant-induced rhinitis,⁹⁹ paradoxical vocal fold motion,¹⁰⁰ hyperventilation syndrome¹⁰¹ and mass psychogenic illness,¹⁰² all of which usually show no evidence of NSBHR.

Occupational causes of irritant-induced asthma

A recent literature review by Baur et al. identified 46 different agents having caused occupational IIA, associated with apparently high-concentration exposures without a latency period.¹⁰³ Almost half their publications were case reports. The most prevalent exposure was from the WTC attacks, which induced very high levels of alkaline dust, which often leads to asthma-like symptoms weeks after the event.⁹⁷ Other causes include diisocyanates (which can induce asthma through both sensitisation and irritant mechanisms), cleaning agents, chlorine, ammonia, sulphur dioxide and diesel exhaust.¹⁰³

Outcomes and management

Following an acute inhalation event to an irritant compound, appropriate management should include rapid removal and protection of the workers from the exposure according to the workplace's guidelines (e.g., use of respiratory protective equipment, evacuation of workplace, decontamination of the injured

workers, eye wash). Limited evidence from case reports suggest that the management of acute IIA is usually the same as the treatment of an acute asthma exacerbation, including bronchodilator therapy and inhaled and/or systemic corticosteroids.^{93,94} Supportive measures, including administration of supplemental oxygen may be needed in the presence of hypoxemia, although limited evidence from animal studies report increased lung injury and worse lung function with the administration of supplemental oxygen.¹⁰⁴ Similarly, an animal study reported that montelukast (a CysLT1 antagonist frequently used in the treatment of asthma) reduces inflammatory markers and AHR in mice following exposure to high-dose chlorine,¹⁰⁵ although montelukast was never studied in humans for the treatment of IIA.

The long-term treatment of IIA is similar to that of non-work-related asthma.⁶⁶ Unlike patients with sensitiser-induced OA, patients with IIA may resume work in their usual workplace with adequate management of their asthma. However, they may develop a worsening of their asthma symptoms with exposure to non-specific irritants in the workplace, significantly affecting their capacity to work.

Similar to what is described in sensitiser-induced asthma after avoidance of the causal agent, up to 75% of patients with acute IIA will have evidence of persistent bronchial hyperresponsiveness several years after an acute symptomatic inhalation accident and will require long-term treatment for their asthma.¹⁰⁶ Of 35 patients with acute-onset IIA, only

17% had normal spirometry and absence of NSBHR at follow-up.

CHALLENGES AND PRIORITIES IN LOW- AND MIDDLE-INCOME COUNTRIES

Worldwide, OA remains underdiagnosed, poorly managed and insufficiently compensated, especially in developing countries.¹⁰⁷ Epidemiological data on OA in low- and middle-income countries are scarce, and likely underestimate its true incidence.¹⁰⁸ Lawin et al. have reported changes in peak expiratory flow suggesting the presence of OA in African workers exposed to polyvinylchloride.¹⁰⁹ However, as pointed out by the authors, a standard investigation of OA was not performed in these workers. The diagnosis of OA includes several steps that may be complex to perform in developing countries. There is a need for implementing tools and training programmes for healthcare workers that may improve diagnosis and care of affected workers from developing countries.¹¹⁰ Creating surveillance programmes in developing countries can also help to identify high-risk industries and guide the establishment of prevention measures.¹¹¹ An isocyanate-induced OA prevention and management programme has been developed and implemented in North America, Europe and Latin America.¹¹² The same type of initiatives need to be extended to low-income countries where the incidence of OA is at risk of increasing due to the growth of the manufacturing sector in these countries.¹¹³

CONCLUSION

WRA remains a significant public health concern, given its high prevalence, long-term respiratory symptoms and significant socio-economic impact on workers and society as a whole. An early and accurate diagnosis is key for allowing the proper management of OA, which begins with suspicion of the diagnosis by healthcare practitioners and workers. As asthma symptoms are non-specific, the diagnosis of sensitiser-induced OA should be achieved with a high level of accuracy through comprehensive investigations in order to avoid unwarranted removal from exposure. A better prognosis is associated with early diagnosis and management, which includes early removal from exposure once sensitiser-induced OA is confirmed. Compared to sensitiser-induced OA, patients with IIA may continue to work in their work environment, as they should not develop WRA symptoms when re-exposed to low doses of the causative agent, although bronchial hyperresponsiveness may affect their capacity to tolerate non-specific irritants in the workplace. Despite optimal management, the majority of workers with OA may still have asthma

symptoms, leading to significant socio-economic consequences.

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R É S U M É

L'asthme professionnel est très prévalant et représente un poids sociétal et financier significatif dans le monde. Cette série d'articles de pointe explore l'épidémiologie, les caractéristiques cliniques, le diagnostic et la prise en charge de l'asthme professionnel (OA), qui comprend l'asthme induit par des sensibilisants/allergènes et des irritants (IIA). Le premier est un développement de l'asthme par la sensibilisation à une substance présente sur les lieux de travail. L'OA est considérablement sous diagnostiqué car ses manifestations cliniques sont non spécifiques ce qui rend son diagnostic difficile. Un diagnostic précoce et exact de l'OA grâce à des tests

complets est primordial pour éviter une éviction injustifiée de l'exposition et permettre une prise en charge rapide des cas confirmés. En dépit d'une prise en charge optimale, près de 70% des patients atteints d'OA auront un asthme persistant plusieurs années après le diagnostic. L'IIA se réfère classiquement à la survenue de novo d'un asthme suivant immédiatement une exposition intense à un agent irritant. Certains cas d'IIA suivant de multiples expositions intensives ou une exposition minime mais chronique ont cependant été rapportés.

R E S U M E N

La prevalencia del asma relacionada con el trabajo es muy alta y representa una importante carga social y económica en todo el mundo. En este artículo de la serie de Artículos Vanguardistas se analizan las características epidemiológicas y clínicas, el diagnóstico y el tratamiento del asma profesional (OA), que incluye el asma inducido por sensibilizantes y el asma inducido por irritantes (IIA). El OA inducida por sensibilizantes consiste en la aparición del asma a partir de la sensibilización a una sustancia en el lugar de trabajo. Este tipo de asma se pasa por alto en gran parte de los casos y sus manifestaciones clínicas son inespecíficas, lo cual dificulta su diagnóstico. Un diagnóstico temprano y

exacto del OA mediante investigaciones exhaustivas es fundamental para evitar un aislamiento injustificado a ciertas exposiciones y facilitar el tratamiento temprano de los casos confirmados. Pese a un manejo óptimo, hasta 70% de los pacientes con OA presentarán asma persistente años después del diagnóstico. El IIA se refiere clásicamente al asma de nueva aparición, que se presenta de forma aguda tras una exposición intensa a una sustancia irritante. Sin embargo, se han comunicado algunos casos de este tipo de asma, tras múltiples exposiciones de alto grado o con una exposición crónica a dosis bajas.
