

Clinical Management Review

Impact of Identification of Clinical Phenotypes in Occupational Asthma

Susan M. Tarlo, MB BS, FRCP(C)^a, and Santiago Quirce, MD, PhD^b *Toronto, ON, Canada; and Madrid, Spain*

Phenotypic differences and similarities in the spectrum of occupational asthma (OA) subtypes reflect the underlying mechanisms of the diverse forms of the disease, and these phenotypes provide information as to diagnostic steps and approaches to management. In large part, the phenotype reflects the existence of immunologic mechanisms and the presence or absence of a specific IgE-antibody response to a work sensitizer. However, further differences occur between OA from high- and low-molecular-weight sensitizers (chemical sensitizers), which potentially might be relevant for nonoccupational asthma. Chemical sensitizers cause a specific response that is more likely to be a late asthmatic response and specific IgE can be identified only in a minority. Irritant-induced asthma is most easily recognized when it occurs with 1 or more high-level respiratory irritant exposure(s) but is also possible with chronic low-level exposures as in cleaners, farmers, and woodworkers, as suggested from epidemiologic studies. OA chronic obstructive pulmonary disease overlap is more common in older patients and with OA from low-molecular-weight sensitizers. Removal from exposure to the causative agent is currently advised for those with OA from sensitization: further studies with omalizumab and other biologic agents are needed to determine whether these might allow return to the same exposure. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Occupational asthma; Work-related asthma; Sensitizers; Irritant-induced asthma; Phenotype; Irritant

INTRODUCTION: DEFINITION AND CLASSIFICATION OF OCCUPATIONAL ASTHMA

The population-attributable risk for incident asthma from occupation has been estimated in a recent official American Thoracic Society Statement to be 16% (95% CI, 10%-22%),¹ on the basis of 9 longitudinal studies of incident asthma. This estimate is similar to earlier estimates,² and indicates that the workplace is an important subset of adult asthma. Understanding the mechanisms and features of occupational asthma (OA) including clinical phenotypes, and identifying the effects of

exposure changes at work, can be helpful not only for improving diagnosis and management of these patients³ (Table 1) but can also lead to better understanding of nonoccupational asthma.

OA is defined as asthma that is caused by work, unlike work-exacerbated asthma, which is worsened by workplace exposures (often on a transient basis) but is not caused by work.⁴ Both OA and work-exacerbated asthma are subsets of work-related asthma (WRA), but this review will focus on OA. OA can be caused by a specific sensitizer at work that is either a high-molecular-weight (HMW) allergen (>10 kd), usually a protein, or can be a low-molecular-weight (LMW) sensitizer, which is usually a chemical agent. In addition, a smaller subset of OA is caused by irritant exposures at work, typically a high-level irritant exposure on 1 or more occasions. This is termed irritant-induced occupational asthma (IIA). Potentially, chronic irritant exposures at work may also cause IIA as suggested from epidemiologic studies, but this cannot be clearly identified in an individual patient.⁵

As will be discussed in this article, the clinical phenotype of OA from an HMW sensitizer, associated with specific IgE antibodies, is very similar to that of nonoccupational allergic asthma, for which it can serve as a model, and pathology is typically eosinophilic. In contrast, although chemical exposures are common outside the workplace setting, recognized asthma due to LMW-sensitizing agents may or may not be associated with eosinophilic inflammation, has generally been limited to occupational cases, and the contribution of chemical sensitizers to asthma outside the workplace is currently unknown. IIA is relatively uncommon but can occur from both occupational and nonoccupational irritant exposures.

OA PHENOTYPES

OA caused by HMW agents

The phenotype of OA caused by an HMW agent is induced by a workplace sensitizer, usually a protein or glycoprotein with the ability to act as a complete antigen and stimulate the adaptive immune system causing allergic sensitization. Thus, it very much resembles the pathogenesis of common allergic asthma. There are more than 500 identified causative agents of OA, and at least 372 HMW allergens have been identified as elicitors of OA by evidence-based medicine.⁶ The pathophysiology usually involves

^aRespiratory Division, Department of Medicine, University Health Network, Toronto Western Hospital, University of Toronto Department of Medicine and Dalla Lana Department of Public Health, Toronto, ON, Canada

^bDepartment of Allergy, La Paz University Hospital, IdiPAZ, and CIBER of Respiratory Diseases CIBERES, Madrid, Spain

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Corresponding author: Susan M. Tarlo, MB BS, FRCP(C), Toronto Western Hospital EW7-449, 399 Bathurst St, Toronto, ON M5T 2S8, Canada. E-mail: susan.tarlo@utoronto.ca.

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Abbreviations used

ACO- Asthma-COPD overlap
 COPD- Chronic obstructive pulmonary disease
 HMW- High-molecular weight
 LMW- Low-molecular weight
 IIA- Irritant-induced occupational asthma
 OA- Occupational asthma
 OACO- Occupational asthma-COPD overlap
 SIC- Specific inhalation challenge
 SPT- Skin prick test
 WRA- Work-related asthma

an IgE-dependent mechanism and activation of the type 2 immunoinflammatory pathway in the airways, with involvement of dendritic cells, mast cells, CD4⁺ T_H2 lymphocytes, B lymphocytes/plasma cells, and eosinophils. Specific IgE antibodies bind to high-affinity receptors in mast cells and basophils and, upon exposure to the sensitizing agent, cause the release of potent proinflammatory mediators and chemoattractant molecules, which result in a dense inflammatory infiltrate of the airways with a predominance of eosinophils. Once this allergic mechanism is initiated, subsequent exposures to very low concentrations of the offending agent are able to elicit asthma symptoms, usually accompanied, and often preceded, by rhinoconjunctivitis.

The diagnosis of IgE-mediated sensitization to HMW agents is made in part by performing skin prick tests (SPTs) or by measuring circulating specific IgE antibodies to workplace allergens. These tests, however, are limited by the lack of standardized and commercially available reagents, and in many instances it is necessary to use home-made allergen extracts following stringent procedures. The quality of the occupational allergen extracts used for SPT is very heterogeneous and the sensitivity of several SPT solutions is low.⁷ Another limitation is that demonstration of IgE-mediated sensitization does not imply clinical relevance, because this phenomenon can be due to cross-reactivity to panallergens or epitopes from unrelated sources, or in some cases, due to latent sensitization without clinical expression.⁸

A systematic review and meta-analysis on 62 studies of OA confirmed by specific inhalation challenge (SIC) and/or peak flow monitoring showed that specific IgE tests had a sensitivity of 0.74 (95% CI, 0.66-0.80) and a specificity of 0.71 (95% CI, 0.63-0.77) for HMW allergens.⁹

There is limited information of the specific components (allergenic molecules) that are causally involved in OA caused by HMW agents, with the exception of natural rubber latex and wheat flour, or in the cases when the allergen source is an isolated protein itself (eg, enzymes such as alpha-amylase, papain, and subtilisin). The identification of the relevant allergenic molecules and the introduction of component-resolved diagnosis could be an important advance to improve the diagnosis of OA.^{9,10}

The diagnosis of OA is most definitively confirmed by SIC: a positive challenge with an HMW agent is commonly manifest by early or dual asthmatic responses, and an increase in fractional exhaled nitric oxide.¹¹ However, because this SIC is available in only a few specialized centers around the world, the combination of sensitization to a workplace agent and nonspecific bronchial hyperresponsiveness has been used as surrogate to establish the diagnosis. A recent non-SIC-based probability model for OA

induced by HMW agents has been suggested, especially when referral to a tertiary center is not possible. This score combines age 40 years or less, work-related rhinoconjunctivitis, inhaled corticosteroid use, agent type, nonspecific bronchial hyperresponsiveness, and work-specific sensitization, with an area under the receiver-operating characteristics curve of 0.91 (95% CI, 0.86-0.95).¹² However, for performance of these tests, patients would likely still need specialist referral, and should still be working for best sensitivity of nonspecific bronchial hyperresponsiveness testing.

OA caused by LMW agents

Several LMW-sensitizing agents (≤ 10 kd) have been recognized to cause OA. The diagnosis has been based on both subjective evidence from the clinical history (asthma worsening at work and improving during periods off work) and objective evidence, most convincingly from blinded SIC with use of nonirritating exposure concentrations of the suspected agent. In some cases, the diagnosis may be supported by changes in serial peak expiratory flow recordings, serial methacholine challenges, and serial measures of induced sputum cytology, comparing results for these performed during work periods with exposure and periods off work or out of exposure.⁴

These investigations have convincingly identified the presence of OA from many LMW sensitizers, and the mechanism is presumed to be from specific immunologic responses. However, this remains a presumption for many agents because there are only a few for which specific IgE antibodies can be identified. In contrast to the sensitivity and specificity of 0.74 (95% CI, 0.66-0.80) and specificity of 0.71 (95% CI, 0.63-0.77) for HMW allergens, a recent systematic review found the sensitivity of specific IgE to be 0.28 (95% CI, 0.18-0.40) and specificity to be 0.89 (95% CI, 0.77-0.95) for LMW agents.⁹ This is perhaps analogous to the clinical difficulty in demonstrating a specific IgE antibody mechanism for presumed allergic responses to most medications. Immunologic support has been provided by demonstration of specific IgE antibodies for some chemical respiratory sensitizers such as acid anhydrides (eg, phthalic anhydride and maleic anhydride) when conjugated with human serum albumin, complex platinum salts (by SPT and serum specific IgE), and nickel and chrome salts. The most common LMW sensitizers in many clinical series have been diisocyanates (eg, toluene diisocyanate, diphenylmethane diisocyanate, hexamethylene diisocyanate, and isophorone diisocyanate). Serum specific IgE antibodies have been demonstrated in a substantial subset (55%) of patients with diisocyanate-induced OA, directed against a conjugate with albumin after exposure to the vapor of the diisocyanate, but only a small proportion of patients if the liquid diisocyanate was used to prepare the substrate.¹³ This illustrates that IgE antibodies may be specific to the physical state of the chemical sensitizer as well as the chemical state, as also has been shown clinically by SIC, for example, in some patients with a positive response to a formaldehyde in a resin dust but not as a gas.^{14,15} For the significant minority of those with diisocyanate-induced OA and no demonstrable specific IgE, there may be IgE antibodies to a substrate that has not been identified, or there may be other mechanisms. Monocyte chemoattractant protein-1 is released from blood of sensitized patients by a conjugate of diisocyanate and human serum albumin with 79% sensitivity and 91% specificity,¹⁶ again supporting a specific immune response (but not necessarily IgE-mediated). In addition, animal

TABLE I. Phenotypes of OA

Comparisons	HMW sensitizer OA	LMW sensitizer OA	IIA	OACO
Mechanism	IgE-mediated	Some IgE-mediated but many unknown mechanisms	Respiratory irritant	HMW, LMW, or IIA, but more common in LMW OA
Duration of exposure before onset	Most within 2 y of first exposure	Most within 2 y of first exposure	Definite IIA, within 24 h of high-level exposure	More common with longer exposure
Some common causes	Flour, animals, plants, foods, enzymes	Diisocyanates, acrylates, epoxy resins, metal salts	Accidental spills, fires	LMW agents, more than HMW agents
Specific IgE	Yes	Only for a few agents	No	Depends on underlying OA
Occupational rhinitis	Most patients and often precedes OA	Common but less than with HMW agents	Not commonly reported	NA
Occupational urticaria	Reported in 15% with OA	NA	NA	NA
Timing of asthmatic response on challenge	Most commonly immediate	Commonly isolated late	Not applicable	Not applicable
Implications for further exposure	Removal	Removal	Continue work but avoid high exposure	Continue work but avoid high exposure

NA, Not available.

studies with several of these agents have shown support for a specific antibody response rather than a nonspecific inflammatory response.¹⁷

Most LMW sensitizers are very reactive chemicals, usually with at least 2 double bonds. These features have led to the development of quantitative structural activity relationship models and other *in vitro* methods as predictive strategies to identify potential sensitizing chemicals^{18,19} for which further validation is required. For an individual patient at work, such as a cleaner, there are often multiple chemical exposures, and even with clear findings of OA it is often difficult to identify the specific causative agent and to identify the specific immunologic mechanism.

The phenotype of OA from most LMW sensitizers has some differences from the allergic phenotype associated with the HMW agents although there can be overlap.²⁰ As recognized for many years, OA from LMW agents is more likely to manifest as a late asthmatic response, onset 4 to 6 hours after exposure, and is often an isolated late response. In the large series reported by Vandenplas et al,¹¹ with positive specific challenges, 66% had a late asthmatic response and in 36% of all LMW OA cases the late asthmatic response was an isolated response with no preceding early response. In contrast, those with OA from an HMW agent more often had an isolated early asthmatic response (49% vs 32% of those due to LMW agents), and only 13% had an isolated late asthmatic response. Other phenotypic differences were found in blood eosinophils and exhaled nitric oxide (fractional exhaled nitric oxide)—both were higher in the HMW group versus the LMW group. Both groups had a rise in fractional exhaled nitric oxide postchallenge although the rise was greater in the HMW group. However, perhaps surprisingly, there was no significant difference in sputum eosinophils or other sputum cytology between groups. Atopy based on skin tests to common allergens was also more common in the HMW group as was preceding rhinitis.¹¹ These phenotypic findings suggest some differences in mechanisms between HMW and LMW agents, but also several common features.

Irritant-induced occupational asthma

IIA presents with a different clinical phenotype on history from OA induced by sensitizers. Clinical features include the

development of new-onset asthma after 1 or more irritant exposures at work. The initially described phenotype, reactive airways dysfunction, was that of asthma starting within 24 hours of a single very high irritant exposure and persisting for at least 3 months, with objective findings of asthma and no evidence of previous lung disease.²¹ The irritant exposure was initially confined to vapors, fumes, or gases, but later this expanded to include irritant dusts, such as from the World Trade Center collapse.²² Subsequent descriptions also modified Brooks et al's criteria²¹ to 1 or more high-level exposures, and the term "irritant-induced" was used to describe cases including those that did not completely fit criteria for reactive airways dysfunction.²³

A later consensus statement on IIA from the European Academy of Allergy and Clinical Immunology⁵ included the above categories but also considered the possibility of IIA from chronic low-level irritant exposures, based on reports of higher than expected rates of asthma in working populations such as cleaners, farmers, and wood workers. Although several studies have shown a statistically significant increase in asthma among these workers, it remains unclear whether this is truly due to chronic irritant exposures or whether an unrecognized higher level irritant exposure may have been the trigger. As acknowledged in the European Academy of Allergy and Clinical Immunology consensus, exposures are generally not measured in the workplace immediately preceding the development of asthma. In addition, in epidemiologic studies, some of these excess cases of asthma may have arisen from an unrecognized HMW or LMW sensitizer. Currently, this concept of possible low-level IIA cannot be proven and is not generally compensable from workers' compensation systems.

Other than the history of exposure and timing of exposure before onset of asthma, the main phenotypic difference from patients with OA from a sensitizer is that patients with IIA from 1 or more high-level exposures do not generally have improvement in asthma symptoms, peak flow readings, and airway responsiveness during periods off work compared with periods at work if the high-level exposure is not repeated. However, ongoing worsening at work and improvement off work can be observed if the patient with IIA has ongoing nonspecific

bronchial hyperresponsiveness and low-level irritants at work exacerbate asthma in the same way as for those with coincidental onset of asthma. Physical examination findings, response to asthma medications, and pulmonary function findings at the time of diagnosis do not differ from other patients with asthma. However, asthma may improve and even resolve after weeks to years in patients with IIA, despite continuing the same work, if they are not exposed to further high-level irritants.

The mechanism of asthma in these patients is assumed to be from airway irritation resulting in an inflammatory and likely neurogenic response that may include activation of transient receptor potential channels, and possible mediation by alarmins.⁵ There are no distinct pathologic changes that are useful for diagnosis although these patients are less likely to have eosinophilic airway inflammatory findings compared with those with OA from an HMW sensitizer.

OA-chronic obstructive pulmonary disease overlap

Asthma and chronic obstructive pulmonary disease (COPD) are 2 common respiratory diseases that can coexist in 15% to 20% of patients.²⁴ Subjects with COPD who show features of asthma, and patients with asthma with a smoking history who develop non—fully reversible airflow obstruction, are categorized as subjects with asthma-COPD overlap (ACO).^{24,25} These subjects have been usually described among patients with COPD in whom a diagnosis of asthma is made on the basis of highly reversible airflow obstruction, type 2 inflammation characterized by airway and/or peripheral blood eosinophilia, or a previous physician diagnosis of asthma.²⁶ However, the prevalence and clinical features of ACO among subjects with WRA remain largely unknown.

A telephone survey conducted in the United States as part of the Behavioral Risk Factor Surveillance Survey found that 51.9% of adults with WRA and 25.6% of adults with non-WRA had ever been diagnosed with COPD. Subjects with concurrent WRA and COPD had more severe exacerbations and asthma outcomes than those with non-WRA and no COPD.²⁷

Ojanguren et al²⁸ conducted a retrospective study in Montreal aiming to identify ACO in subjects with OA and to compare the clinical characteristics of patients with OA with or without ACO. Of the 304 subjects who were included, 86.2% were diagnosed with OA and 13.8% with occupational ACO (OACO), prevalence that is similar to the lower estimates of ACO among patients with asthma.^{25,26} Subjects with OACO were older, received higher doses of inhaled corticosteroids, and were less atopic than subjects with OA.²⁸ No statistically significant differences were observed between both groups in the inflammatory pattern in sputum before or after SIC. Subjects with OACO had been exposed to the offending agent for a longer duration of time and were more frequently exposed to LMW agents (70% vs 52%) than subjects with OA.

A study carried out in Finland showed that the risk of ACO was significantly related to the presence of mold odor in the workplace, but not to other dampness indicators.²⁹ Another Finnish study suggested that patients with asthma with occupational exposure to vapors, gases, dust, or fumes develop ACO more often than subjects without such exposure.³⁰ Similarly, workers such as cleaners, and first responders at the World Trade Center collapse, who have increased risk for IIA, are also at increased risk for OACO,^{31,32} either from the underlying irritant

exposure and preexisting/coincidental asthma, or possibly as a component of chronic IIA.

STRATEGIES FOR MANAGEMENT AND PREVENTION

The phenotypic differences between OA from a sensitizer versus IIA are associated with significant differences in management and preventive strategies for OA.^{33,34}

Primary prevention measures are most effective when feasible. Ideally, sensitizers would be removed from workplaces and substituted with nonsensitizing agents. A good example is the removal of powdered latex gloves and use of nonlatex gloves for housekeeping work. When latex gloves cannot be replaced, then a change to powder-free, low-protein latex gloves has also been effective, and these measures have essentially prevented OA from natural rubber latex. Encapsulation of powdered enzymes in the detergent industry also has been an effective preventive measure, and risks of sensitization for animal care workers have been reduced by measures to reduce allergen exposure, for example, by negative pressure ventilation for cage-changing. For LMW agents similarly, measures include removal when possible, for example, replacement of a diisocyanate-containing paint with a nonurthane paint. Removal of aldehydes for medical equipment sterilization and replacement with hydrogen peroxide and acetic acid was expected to reduce risk, but a recent case report has suggested development of OA from this, possibly by sensitization.³⁵ Reducing exposure by occupational hygiene measures such as improved ventilation, containment, and finally use of respiratory protective equipment is less effective but can also be helpful in reducing the risk of sensitization.³⁶ Worker education is an important component to understand risks^{37,38} and improve adherence to occupational hygiene measures. High irritant exposures (that can cause IIA) are usually accidental, but primary preventive measures may include premixing of cleaning products or other products, appropriate occupational hygiene measures, worker knowledge of potential risks from a spill/accident, and knowledge of appropriate action to take to reduce exposure in the event of a spill/accident.³³

Secondary prevention for OA from a sensitizer can be effectively added to primary measures, as in enzyme manufacturing industries³⁹ and diisocyanate workers.³⁶ This includes surveillance measures, such as air monitoring to ensure exposure levels are not exceeded, and medical surveillance to detect OA early, by preplacement and regular respiratory questionnaires, specific IgE testing (when feasible), for early detection of specific sensitization and potential relocation of sensitized workers (with or without occupational rhinitis), and spirometry, with adherence to recommended technical performance.^{40,41} Education of workers is also an important component of secondary prevention for all phenotypes of OA, including IIA, which may lead to earlier diagnosis and prompt recognition that symptoms may be caused by work and result in earlier investigation with the health care provider.

Tertiary prevention consists of early diagnosis and appropriate management of the patient with OA. Again, this differs on the basis of phenotype of OA. For those with OA from a sensitizer, early diagnosis and complete removal from the sensitizing agent provide a better medical outcome,^{42,43} but can be associated with significantly reduced socioeconomic effects.⁴⁴ Other factors associated with more severe sensitizer-induced OA outcome are

lower education level and ethnicity.⁴³ In contrast, many with IIA can often continue the same work if their asthma can be well controlled, but some with ongoing exacerbations at work may require modified work. Additional management as for nonoccupational asthma includes appropriate environmental changes and pharmacologic management. There may be a role for omalizumab⁴⁵ and other biologic agents in some patients as suggested by small studies, but additional studies are needed to determine whether these might prevent the need for exposure cessation, and to assess cost-effectiveness. Support should be provided for a workers' compensation claim as appropriate for all patients with OA, and the diagnosis should be recognized as a "sentinel event" requiring notification of those who may intervene in the workplace to identify other affected workers and reduce risks for coworkers.⁴⁶

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