

Occupational asthma: Current concepts in pathogenesis, diagnosis, and management

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Activity Objectives

1. To become familiar with the revised classification and nomenclature for occupational asthma (OA) outlined in recent consensus guidelines.

2. To review the various subtypes of respiratory illnesses categorized under the board heading of work-related asthma (WRA).

3. To review current theories of the pathogenesis and risk factors of WRA.

4. To provide evidence-based recommendations for diagnosis and management of OA.

5. To review prognostic indicators of OA.

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Occupational asthma (OA) may account for 25% or more of *de novo* adult asthma. The nomenclature has now better defined categories of OA caused by sensitizing agents and irritants, the latter best typified by the reactive airways dysfunction syndrome. Selecting the most appropriate diagnostic testing and management is driven by assessing whether a sensitizer is involved, and if so, identifying whether the sensitizing agent is a high-molecular-weight agent such as a protein or a low-molecular-weight reactive chemical such as an isocyanate. Increased understanding of the pathogenesis of OA from reactive chemical sensitizers is leading to development of better diagnostic testing and also an understanding of why testing for sensitization to such agents can be problematic. Risk factors for OA including possible genetic factors are being delineated better. Recently published guidelines for the diagnosis and

management of occupational asthma are summarized; these reflect an increasingly robust evidence basis for recommendations. The utility of diagnostic tests for OA is being better defined by evidence, including sputum analysis performed in relation to work exposure with suspected sensitizers. Preventive and management approaches are reviewed. Longitudinal studies of patients with OA continue to show that timely removal from exposure leads to the best prognosis. (J Allergy Clin Immunol 2009;123:519-28.)

Key words: Occupational asthma, irritant-induced asthma, sensitizer-induced asthma diagnosis, isocyanates, management, guidelines, RADS

Several terms are now used to define subsets of patients with *work-related asthma* (WRA), a broad term that refers to asthma that is exacerbated or induced by inhalation exposures in the workplace. The nomenclature of work related asthma has been evolving, so medical literature and studies must be considered in that context. Occupational asthma (OA), a subset of WRA, has been the subject of a number of recently published reviews and guidelines.¹⁻⁷ As defined by the 2008 Guidelines of the American College of Chest Physicians (ACCP), WRA includes OA that refers to *de novo* asthma or the recurrence of previously quiescent asthma induced either (1) by sensitization to a workplace substance, termed *sensitizer-induced OA*, or (2) by exposure to an

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Abbreviations used

ACCP:	American College of Chest Physicians
ENO:	Exhaled nitric oxide
HMW:	High molecular weight
HSA:	Human serum albumin
LMW:	Low molecular weight
MSDS:	Material Safety Data Sheet
OA:	Occupational asthma
PEFR:	Peak expiratory flow rate
RADS:	Reactive airways dysfunction syndrome
SIC:	Specific inhalation challenge
TDI:	Toluene diisocyanate
TMA:	Trimellitic anhydride
WEA:	Work-exacerbated asthma
WRA:	Work-related asthma

inhaled irritant at work, termed *irritant-induced OA*. Previously, OA was defined to refer only to sensitizer-induced OA. A distinct subset of WRA is work-exacerbated asthma (WEA), defined to be present in workers with pre-existing or concurrent asthma that is triggered by work-related factors (eg, aeroallergens, irritants, or exercise), but not considered to be OA. Estimates of the incidence and prevalence of OA vary. It has generally been accepted that at least 9% to 15% of adult asthma can be attributed to workplace exposures, although recent data indicate that 25% or more of *de novo* asthma may have an occupational basis.^{1,2} WRA results in considerable morbidity to affected individuals, but also results in tremendous costs to society.² Failure to recognize OA in a timely fashion can lead to permanent respiratory impairment, underscoring the need for early diagnosis and intervention.

TYPES OF OA**Sensitizer-induced OA**

Occupational asthma from sensitizers typically presents with a latent period of exposure, followed by the onset of clinical disease. After sensitization, airway reactions develop from levels of exposure to the sensitizing agent that were tolerated before sensitization. Although the mechanism causing OA from some sensitizers has been demonstrated to have an immunologic basis (IgE antibody-mediated or otherwise), no immunologic mechanism has been demonstrated for some suspected sensitizers (eg, colophony). OA sensitizers (Table I) may be categorized on the basis of their molecular weight. By convention, high-molecular-weight (HMW) sensitizers are >10 kd, with common examples being inhaled protein agents. HMW agents typically cause occupational asthma by IgE antibody-mediated mechanisms. Low-molecular-weight (LMW) sensitizers are often reactive chemicals that act as haptens in that they can only induce an adaptive immune response and be recognized as antigens after combining with self-proteins to form immunogenic conjugates after inhalation. Some LMW agents have been demonstrated to cause sensitization via IgE-mediated mechanisms, whereas have not. There are more than 250 reported workplace sensitizers.

Irritant-induced OA

Not previously considered a form of occupational asthma, *de novo* asthma caused by exposure to inhaled irritants at work now is commonly termed *irritant-induced OA*.²

The existence of the reactive airways dysfunction syndrome (RADS) resulting from a single episode of a high level exposure to

an irritant agent (usually from an occupational accident) has long been recognized.^{2,8} Examples of agents reported to cause RADS include chlorine gas, hydrochloric acid, anhydrous ammonia, hydrogen sulfide, fumigating fog, heated acids, and smoke by inhalation. In 1984, a toxic cloud of methyl isocyanate gas released from a chemical plant in Bhopal, India, killed thousands of people, and caused thousands more to develop persistent respiratory disease, some with reversible airway obstruction. After the collapse of the World Trade Center towers in New York City during the 2001 terrorist attacks, a complex mixture of airborne dusts and pollutants was elaborated that has been associated with RADS (and other respiratory disorders) in exposed rescue and recovery workers and residents of the surrounding area.⁹

The 2008 ACCP consensus guidelines retain use of the RADS term, but consider it to be a form of irritant-induced asthma.² By definition, the diagnosis of RADS can be made only when defined criteria are satisfied and should not be made in patients with pre-existing asthma (Table II). This leaves open another debate about how to define worsening of pre-existing asthma caused by inhalation of high levels of irritants or worsening of pre-existing smoking-related chronic obstructive pulmonary disease.

There is still controversy about whether chronic lower-level exposure to irritants can cause OA.^{2,5} Repeated peak exposure to irritant gases in the pulp industry has been shown to increase the risk for both adult-onset asthma and wheezing.¹⁰ There is also a report that asthma symptoms developed in 3 patients after repetitive exposure to irritants that occurred over several days to months.¹¹ According to the 2008 ACCP guidelines, cases that do not meet the stringent criteria for RADS (eg, when there is several-day lag 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) are all classified under the general category of irritant-induced asthma. Specific examples include meat wrapper's asthma, pot room asthma, asthma from professional cleaning materials, and asthma from exposure to ozone, endotoxin, formaldehyde, and quaternary ammonium compounds.

PATHOPHYSIOLOGY**Pathophysiology of sensitizer-induced OA**

OA from HMW sensitizers. High-molecular-weight agents such as proteins and glycoproteins (Table I) characteristically act as complete antigens that cause sensitizer OA through a classic IgE antibody-mediated mechanism. The allergens responsible for OA from some HMW agents have been well characterized—for example, in detergent workers who develop asthma from exposure to *Bacillus subtilis* enzymes, or in egg processing workers. However, identifying the actual protein sensitizers in complex plant or animal materials can be problematic, confounding studies about the pathogenesis of OA and development of appropriate agents for diagnostic testing. For example, baker's asthma caused by wheat inhalation typically does not occur because of sensitization to wheat ω -5 gliadin [Tri a 19], an allergen commonly important for wheat allergy from oral ingestion such as food allergy in children or wheat-dependent exercise-induced anaphylaxis. Instead, baker's asthma may be caused by an increasingly recognized number of other allergens present in wheat flour (eg, α -amylase inhibitors, thioredoxins cross-reactive with grass allergens, a wheat lipid transfer protein, Tri a 14, a wheat serine proteinase inhibitor, and baking additives such as fungal α -amylase

TABLE I. Examples of sensitizers reported to cause OA

Agent	Industry, process, or occupation
High molecular weight	
Animal and insect-derived	
Bird proteins (feathers, serum)	Bird breeders
Crustaceans: snow crab, prawn	Seafood processors
Eggs (chicken)	Food processors
Insects	Beekeepers, farmers, granary workers, silk processing, dockworkers
Mammalian proteins in hair, dander, urine	Research labs, veterinarians, breeders, pet shop workers
Pharmaceutical enzymes, eg, pancrease	Pharmaceutical industry, health care workers
Sea squirt (oyster parasite)	Oyster processing workers
Bacterial and fungal-derived	
<i>Bacillus subtilis</i> -derived enzymes	Detergent formulators
<i>Penicillium caseii</i>	Cheese workers
Thermophilic molds	Mushroom workers
Plant-derived	
Henna dye	Beauticians
Latex, natural rubber	Health care workers
Plant enzymes (papain, bromelain)	Food, pharmaceutical industries
Psyllium	Laxative manufacture, nursing
Vegetable gums (arabic, guar, tragacanth)	Printing/bookbinders, food, carpet manufacture
Wheat flour	Bakers
Low molecular weight	
Persulfates (in hair bleaching solutions)	Hairdressers
Metals and metal salts	
Chromium	Miners and cement, electroplating and tanning workers
Cobalt	Metal workers and diamond polishers
Nickel sulfate	Metal plating
Platinum	Alloy makers
Organic chemicals	
Acid anhydrides (prototype: trimellitic anhydride)	Plastics industry, dye, insecticide makers, organic chemical manufacture (used in epoxy resins)
Acrylates, methacrylate (artificial nail glue)	Printing industry, beauticians
Ethylenediamine	Shellac/lacquer industry workers
Paraphenyldiamine in hair dye	Hairdressers
Polyisocyanates (prototype: toluene diisocyanate)	Polyurethane, foam coatings, adhesives production, and end-use settings (eg, spray painters, foam workers)
Pharmaceuticals (antibiotics, cimetidine)	Hospital and pharmaceutical workers
Relevant components uncertain	
Wood dusts (red cedar, oak, mahogany, redwood, iroko)	Foresters, woodworkers and furniture makers

[Asp o 21]).¹²⁻¹⁴ It is unclear why some allergens are more important for developing IgE-mediated sensitivity to wheat from inhalational exposure, whereas others are important for oral ingestion.

Baker's asthma also provides an example of OA from HMW sensitizers that may have a more complex cascade of events related to IgE-mediated sensitivity than would be expected from what is known about nonoccupational allergic asthma to common aeroallergens. Using serum from patients with baker's asthma, IgE binding inhibition studies have demonstrated that thioredoxin wheat allergens can have partial cross-reactivity with endogenous human thioredoxins in lungs. It has been hypothesized that the sharing of B-cell epitopes by cereal and human thioredoxins could provide the potential for molecular mimicry/cross reactivity, with consequent cross-linking of thioredoxin-specific IgE by human thioredoxin. It is speculated that this might induce mediator release and inflammatory processes without external exposure and be a mechanism by which there might be maintenance and deterioration of allergic lung inflammation once baker's asthma has developed.¹²

Eosinophils typically characterize airway inflammation observed in most OA from HMW sensitizers, in contrast with

inflammation seen in OA from some LMW sensitizers that may be more likely characterized by neutrophils.¹⁵

OA from LMW sensitizers. In contrast with the typically IgE-mediated mechanism of OA caused by HMW agents, IgE antibody appears to be of key relevance to the pathogenesis of OA from only some LMW agents. LMW agents that cause OA through IgE-mediated mechanisms include phthalic anhydride; trimellitic anhydride (TMA); complex salts of metals such as platinum (including hexachloroplatinate salts that are immunogenic without need for protein conjugation), chromium, and nickel; epoxy amines; and penicillin.^{2-6,16} Other LMW agents may lead to airway sensitization through non-IgE-mediated immunologic mechanisms that are not completely understood.

Acid anhydrides. Trimellitic anhydride (encountered in plastics, epoxy resins, and drug manufacture) is the best described model of a LMW agent that causes OA through an IgE antibody-mediated mechanism. Positive immediate skin tests to trimellityl-human serum albumin (HSA) and *in vitro* tests for IgE to trimellityl-HSA correlate well with OA, as do immediate skin tests and *in vitro* tests to other acid anhydrides that cause OA. It has been demonstrated that after sensitization, there is antigen

TABLE II. Diagnostic criteria for RADS

1. There is an absence of pre-existing respiratory disorder, asthma symptomatology, or a history of asthma in remission and an exclusion of conditions that can simulate asthma.
2. The onset of asthma occurs after a single exposure or accident.
3. The exposure is to an irritant vapor, gas, fumes, or smoke in very high concentrations.
4. The onset of asthma symptoms develops within minutes to hours and <24 h after the exposure.
5. There is a positive methacholine challenge test finding or equivalent test, which signifies hyperreactive airways, after the exposure.
6. There may or may not be airflow obstruction confirmed with pulmonary function testing.
7. There is exclusion of another pulmonary disorder that explains the symptoms and findings.

Reprinted with permission from Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians consensus statement. *Chest* 2008;134(3 Suppl):1S-41S.² Adapted with permission from Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376-84.⁸

recognition not only of epitopes of the trimellityl hapten but also of new antigenic determinants formed during the conjugation of TMA to protein.¹⁷ Novel mechanisms can promote immediate-type hypersensitivity reactions from TMA. As 1 example, inhaled TMA reacting with any IgE antibody bound to mast cells in the airways could produce trimellityl-modified IgE conjugates that would be recognized as antigenic targets by antitrimellityl IgG antibodies, resulting in IgE cross-linking and mast cell activation.

Polyisocyanates. Low-vapor polyisocyanates and their prepolymers are sensitizers widely encountered in paints and varnishes, elastomers, and the manufacture of flexible and rigid foams and fibers. For brevity, these agents are referred to as *isocyanates*, although methyl isocyanate, a lethal toxic gas (discussed under Irritant-induced OA section), is not a known sensitizer. Although there is incomplete understanding of the pathophysiology of OA from many LMW sensitizers, studies of OA from isocyanates—chemicals that are some of the most common causes of OA—have provided important insights about putative non-IgE-mediated mechanisms in OA. Specific IgE antibodies to isocyanates are present in only a minority of affected patients with OA from toluene diisocyanate (TDI), although they are more commonly present in OA from hexamethylene diisocyanate, indicating that non-IgE antibody-mediated immunologic mechanisms may be of relevance in many patients.¹⁸ Nonetheless, the presence of IgE to isocyanates is a relatively specific marker for isocyanate-induced asthma demonstrated by specific bronchial challenge.¹⁹

In contrast with specific IgE, IgG to isocyanates is a more sensitive but less specific marker for OA from isocyanates. IgG to isocyanates is not thought to cause OA from isocyanates but is best viewed as a marker of exposure. Temporally, serum levels of IgE specific for TDI decline over time after TDI exposure ends, whereas IgG to TDI does not.²⁰ Recently, it has been shown that assays for specific IgE to TDI-albumin conjugates are improved by preparing conjugates in an optimal substitution ratio to avoid oversubstitution of the hapten, which can lead to many false-positive results.^{21,22}

Several non-IgE-mediated immunologic mechanisms have been implicated. In patients with OA to isocyanates, cocubation of PBMCs with diisocyanate-HSA increases secretion of monocyte chemoattractant protein 1.²³ Diisocyanate-HSA-stimulated production of monocyte chemoattractant protein 1 by peripheral blood monocytes has a reported sensitivity of 79% and specificity of 91% in patients with isocyanate OA, far superior to the sensitivity and test efficiency of serum assays for isocyanate-specific antibodies.

In patients with OA from isocyanates who did not have serum IgE to isocyanates, bronchial challenge with isocyanates can generate CD4-positive, IL-5-positive, and CD25-positive lymphocytes in bronchial mucosa, but in the absence of expression of

ε heavy-chain and IL-4 mRNA that would typically occur during the generation of IgE antibody.²⁴ In mouse models of diisocyanate-induced asthma, exposure to isocyanates induces a mixed T_H1/T_H2 response with production of IFN-γ, IL-4, IL-5, and IL-13, but supports the view that isocyanate asthma is driven primarily by CD4⁺ T cells.^{25,26}

Isocyanate exposure also can elicit overproduction of matrix metalloproteinase 9, a finding of potential pathogenetic relevance because of the role of metalloproteinases in the structural changes of asthma.²⁷ Although eosinophilic inflammation may occur in OA from isocyanates, an increase in sputum neutrophils may actually be a more prominent feature of airway inflammation after acute inhalation of isocyanates.²⁸ Mechanistically, this might be partly explained by the observation that on exposure to isocyanates, peripheral mononuclear cells from patients with OA to isocyanates produce IL-8, a chemokine chemoattractant for neutrophils.²³ Neutrophilic airway inflammation has also been found in some groups with nonoccupational asthma, particularly those with more severe disease,²⁹ suggesting that these asthma subsets and isocyanate asthma may share some mechanisms that drive neutrophilic inflammation.

Pathophysiology of irritant-induced OA

In RADS, high levels of irritant exposure initiate an incompletely understood cascade of events that involves innate, non-adaptive immune responses and begins with bronchial epithelial injury. The injury impairs intrinsic respiratory epithelial function and initiates epithelial cell release of inflammatory mediators with putative direct activation of nonadrenergic, noncholinergic pathways via axon reflexes, neurotransmitter release, and resultant neurogenic inflammation. Nonspecific macrophage activation and mast cell degranulation may also occur with the release of proinflammatory chemotactic and toxic mediators. The resultant inflammatory response is then thought to culminate in airway remodeling that includes subepithelial thickening and alteration of mucous glands and smooth muscle structure.³⁰

It is unclear whether components of the hypothesized pathogenesis of RADS have relevance to asthmalike reactions from low-level exposures to respiratory irritants. There is evidence that occupational respiratory irritants may cause reflex bronchospasm with cholinergic neurogenic mechanisms.³¹

EPIDEMIOLOGY AND RISK FACTORS

Other than the intrinsic physicochemical and immunogenic properties of agents, the most important risk for developing OA is the level and duration of exposure to agents capable of causing OA.³² Although tobacco smoking not been found to be

consistently associated with increased risk for OA,³³ reports of an association between smoking and OA from certain agents suggest that the absence or presence of such an association may vary depending on the agent. Atopy is a risk factor for OA from HMW allergens, but with some exceptions, generally not for OA from LMW allergens.

The presence of occupational rhinitis and conjunctivitis may identify patients at greater risk for developing OA. In a case series of 25 employees with TMA-induced OA, 22 subjects had both rhinitis and asthma. In 17 of those (77%), the rhinitis symptoms preceded the respiratory symptoms. In 14 of 17 employees with conjunctivitis symptoms (82%), eye symptoms preceded the OA symptoms.³⁴ Among Finnish patients with confirmed occupational rhinitis, 156 of 420 cases (37%) with asthma were recognized cases of OA. The crude relative risk of asthma was 5.4 for those with occupational rhinitis accepted for compensation.³⁵

Putative genetic factors have recently been identified that may alter risk for OA, although most studies have been conducted in limited populations, and reported associations with many implicated genes have not been replicated. Examples of putative genetic risk factors include HLA class II alleles that may influence the risk of OA from LMW sensitizers or HMW sensitizers such as laboratory animals.³⁶⁻³⁹ In white subjects in Northern Italy, it has been reported that there was a significant positive association between TDI-induced OA with HLA-DQA1*0104 and DQB1*0503, and a protective association between disease and HLA-DQA1*0101 and DQB1*0501.⁴⁰ However, studies in Germany and the United States were unable to find similar associations.^{41,42} In a Korean population, a significant association was found between TDI-OA and the DRB1*15-DPB1*05 haplotype.⁴³ It has been suggested that the differences in conclusions of such studies may be a result of geographical differences between the 2 study populations, small sample size, or phenotyping methods.³⁸ Polymorphisms of glutathione S-transferase may affect risk for OA from isocyanates, with homozygosity for the glutathione S-transferase allele GSTP1*val conferring protection against TDI-induced asthma.³⁸ Other HLA associations have been reported in platinum-sensitized and TMA-sensitized workers.

Although different occupations and exposures certainly influence the risk of OA, there can be great geographical variations in reported risk even in the same occupation. For example, occupational exposures in hairdressers (with persulfate sensitization as a major cause, and other causes being paraphenyldiamine and henna) are commonly reported causes of OA in some countries but not in other countries.⁴⁴ It is speculated that geographical variations in reported asthma may be a result of variations in occupational exposures, differences in coexposures (allergens, pollutants, and susceptibility), or differences in recognition of exposures or relation of exposure to OA.

It has been generally estimated that as many as 25% of adult patients with asthma have WRA, including both OA and WEA.^{1,2} Estimates of the incidence and prevalence of OA are confounded by differing definitions of OA and diagnostic criteria, varying levels and duration of different types of occupational exposure, and limited prospective surveillance data. Estimates of asthma in the workplace and occupational asthma come from 2 basic approaches: (1) population-based studies and surveillance systems, or (2) medicolegal statistics. These approaches often produce different figures because medicolegal statistics are more likely to rely on objective confirmation of cases, whereas population-based studies and surveillance systems tend to identify workers

with probable rather than confirmed OA.⁴⁵ Malo and Gautrin⁴⁵ point out that ideally, the population approach is transformed into a stepwise diagnostic process by increasing the number of tests to lead progressively to identification of cases (Fig 1). Population-based studies and surveillance approaches may underestimate asthma, because workers developing respiratory symptoms may leave an occupation without formally reporting the disease, a so-called *survivor bias*.

A recently published, large-scale study prospectively followed 6837 participants from 13 countries, previously in the European Community Respiratory Health Survey (1990-1995), who did not report respiratory symptoms or a history of asthma at the time of first study.⁴⁶ Asthma was assessed by methacholine challenge test and by questionnaire data on asthma symptoms. At follow-up about a decade later, the risk for adult asthma because of occupational exposures ranged from 10% to 25% (incidence of new-onset occupational asthma of 250-300 cases/million/y), suggesting that the frequency of occupational asthma is systematically underestimated. The study found that asthma risk was increased in workers who reported an acute symptomatic inhalation event such as a fire, mixing cleaning products, or chemical spills (relative risk, 3.3; 95% CI, 1.0-11.1; $P = .051$), consistent with a history of RADS. Occupations with the highest risk were printing, woodworking, nursing, agriculture and forestry, cleaning and caretaking, and electrical processing. The highest risks were associated with exposure to HMW agents, but LMW agents and irritants (eg, isocyanates, latex, cleaning products) were also major contributors to OA. The principal limitations of the study were that analyses of specific occupations and exposures were sometimes based on small numbers, duration of exposure was not fully captured, and assessment of specific IgE (eg, for HMW sensitizers) was not performed.

DIAGNOSIS

Although the diagnosis and management of OA can be complex, published guidelines provide a logical, structured approach (Fig 2). In summary, it is first necessary to establish that a patient has asthma, then that OA is present. A combined approach of using history and objective testing is important for increasing the reliability of the assessment of possible OA.

History

Evaluation of patients with asthma of working age should include information about asthma symptoms and identify any temporal relationships between asthma symptoms and work.

The 2008 ACCP guidelines² also recommend that the following key questions be posed:

- Were there changes in work processes in the period preceding the onset of symptoms?

Importance: Changes in work processes could expose the worker to a new agent or to higher levels of an agent that was previously present. Sensitizing agents carry the greatest risk for sensitization and OA during the first few years of exposure, although the latent period of sensitization can vary and continue many years after exposure begins.⁴⁷

- Was there an unusual work exposure within 24 hours before the onset of initial asthma symptoms?

Rationale/importance: A spill or other high-level exposure to a potentially irritant chemical or chemicals, especially within 24 hours before the first asthma symptoms, raises the suspicion of RADS/irritant-induced asthma (Table I).

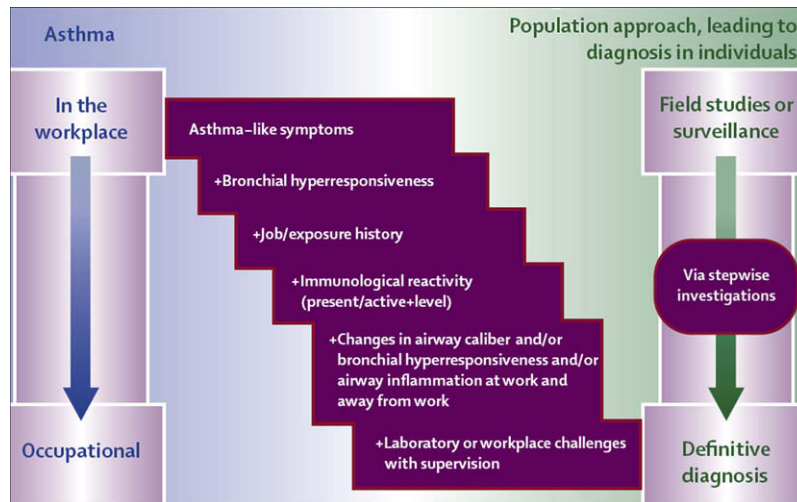


FIG 1. Steps in assessment of workplace asthma. Increasing number of tests progressively leads to identification of cases of occupational asthma and transforms population approach into diagnostic process. Reprinted with permission from Malo JL, Gautrin D. From asthma in the workplace to occupational asthma. *Lancet* 2007;370:295-7.⁴⁵

- Do asthma symptoms differ during times away from work such as weekends or holidays?

Rationale/importance: A positive response is sensitive for identifying OA and should warrant further evaluation by objective means. However, a positive response does not discriminate well between OA and nonoccupational asthma, leading to an incorrect diagnosis in 26% of suspected cases in 1 series.⁴⁸ A negative response may not entirely exclude OA, particularly in a subset of patients with more severe and longstanding cases of OA, in which asthma will not improve or may even worsen, despite removal from work.⁴⁹ The temporal relationship between work shifts and symptoms may be complicated in OA from LMW sensitizers, because airway responses are often isolated late responses (eg, 4-8 hours after exposure) and may present as evening cough or other asthma symptoms after work.

- Are there symptoms of allergic rhinitis and/or conjunctivitis symptoms that are worse with work?

Rationale/importance: These symptoms may start before or have onset concurrent with development of OA.^{34,35} In the presence of possible WRA symptoms, additional work-related symptoms of allergic rhinitis increase the probability of OA from HMW (although not consistently from LMW) sensitizers, whereas work-related dysphonia (suggestive of vocal cord dysfunction) is negatively associated with OA.⁵⁰

A full history for suspected OA should include a history of job duties, exposures, industry, use of protective devices/equipment, and the presence of respiratory disease in coworkers. It is also important to obtain a complete chronological work history from the very first job until the present one to determine whether there could have been previous exposure (and possible sensitization) to agents similar to those in the current workplace. Guidelines recommend that the onset and timing of symptoms, medication use, past lung function, and their temporal relationship to periods at and away from work should be recorded.

Material safety data sheets

The US Occupational Safety and Health Administration requires that suppliers include a Material Safety Data Sheet

(MSDS) with each shipment of an industrial material or chemical, and workers are entitled to receive copies of these sheets. MSDSs can contain information useful in identifying respiratory hazards in the workplace. However, MSDSs may omit information about generic chemical names and formulas, omit disclosure of potential respiratory and skin-sensitizing agents, fail to update current permissible exposure levels, and fail to include documented clinical information regarding specific occupational lung or cutaneous diseases.⁵¹ Nonetheless, identification of a suspect agent from MSDS review can focus subsequent literature review to obtain additional information.

Objective testing

Although objective testing is important in establishing the diagnosis of OA, it should be recognized that all tests have potential false-positive and false-negative responses.

Spirometry and peak expiratory flow rates

Work-related changes in spirometry or peak flow can help establish the diagnosis of OA, although they are effort-dependent and require patient cooperation. Guidelines recommend consideration of a data logger to record measurements as useful in preventing fabrication of peak expiratory flow rates (PEFRs). In 1 study, PEFRs obtained every 2 hours compared with PEFRs obtained 4 times daily had similar sensitivity and specificity in diagnosing OA from sensitizers, but PEFRs measured less than 4 times a day were less effective.⁵²

Current guidelines recommend that there should be a recording period of 4 weeks, including a period of at least 1 week away from work, as the minimum time necessary to identify reliably changes caused by work. However, several work-related patterns can be seen: (1) diurnal worsening during a work day that does not worsen progressively during the work week and improves on the weekend or other days off work, (2) a diurnal pattern of worsening during the working day with the daily value before the work shift value falling progressively over the work week and worsening over successive weeks of work, and (3) an intermittent fall in peak flows during working weeks with

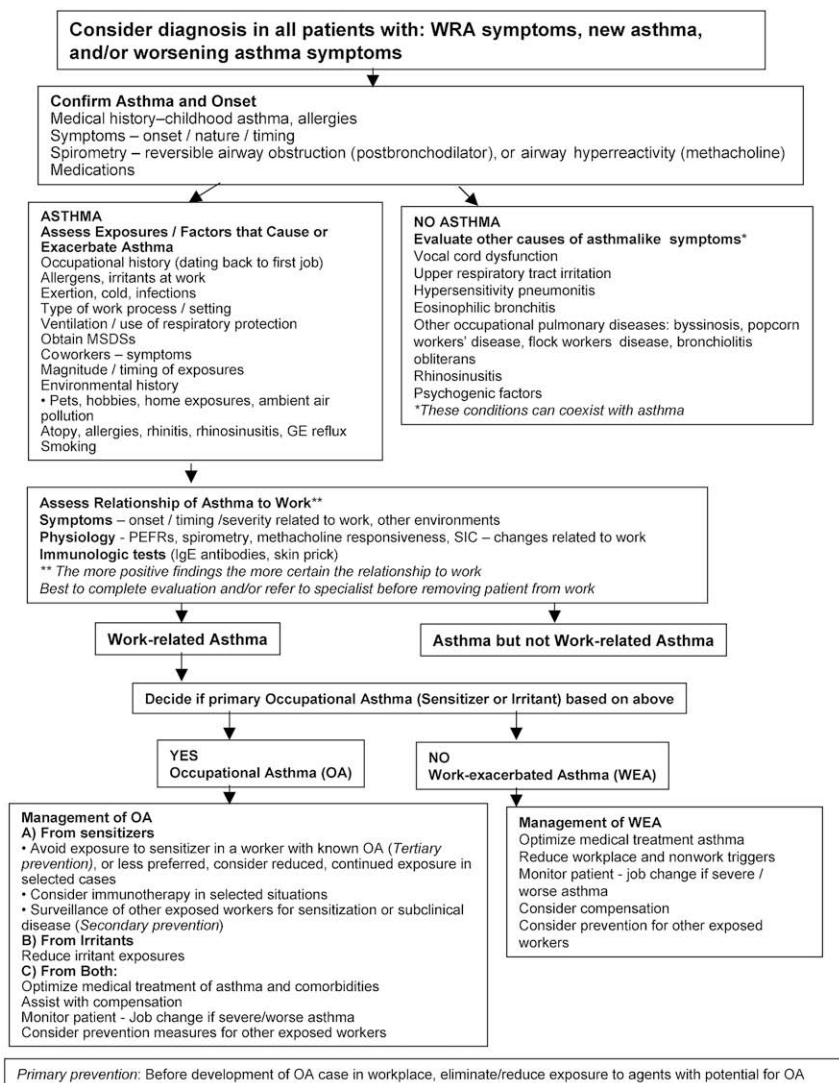


FIG 2. Summary flow chart of WRA. Adapted with modification from Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians consensus statement. Chest 2008;134(3 Suppl):1S-41S.² GE, Gastrointestinal.

marked improvement after several days away from work.² A typical pattern of OA is for patients to be much better on Mondays and get worse as the week progresses, reflected in serial pulmonary function changes. In contrast, the asthmalike condition of byssinosis (caused by inhaling particles of cotton, flax, hemp, or jute) may present with a different pattern of workers being worst on Mondays, but improving as the work week progresses.

The sensitivity and specificity of work-related PEFr assessments in comparison with specific inhalation challenge (see Specific inhalation challenge later) can be high, with pooled estimates of 64% sensitivity (95% CI, 43% to 80%) and 77% specificity (95% CI, 67% to 85%).⁴⁹

Nonspecific airway hyperresponsiveness

Although there are rare reports of OA from isocyanates that are not associated with airway hyperresponsiveness to methacholine,⁵³ a negative test performed proximate to workplace exposure essentially rules out OA from sensitizers.² However, positive

methacholine tests may be present in a number of conditions other than asthma, including recent viral respiratory tract infections, tobacco abuse, chronic bronchitis, and atopy without asthma.⁵⁴ Current guidelines suggest the use of a methacholine or histamine challenge performed toward the end of a work week, with a repeated study at the end of a period (usually ≥ 10 -14 days) away from the exposure. A worsening of PC₂₀ at work versus off work (beyond a 3-fold or greater change in PC₂₀) provides additional evidence to support the diagnosis of sensitizer-induced OA.^{2,55} A methacholine challenge result can revert to normal away from occupational exposure.⁵⁶

Specific inhalation challenge

Specific inhalation challenge (SIC) exposes workers to a suspect OA sensitizer in a controlled setting to demonstrate a direct relationship between exposure to a test agent and an asthmatic response. Although considered a reference standard for identifying OA from a sensitizer, SICs to LMW agents are performed in only a limited number of centers in the world.

Immunologic testing

Because of its high negative predictive value, a negative percutaneous test to a validated occupational protein allergen test reagent generally can exclude OA caused by that allergen with high accuracy.^{2,57} Percutaneous testing with a panel of common aeroallergens can assess whether nonoccupational allergens (eg, household pets) are contributing to a patient's asthma. As mentioned, OA from some LMW sensitizers may be associated with specific IgE antibody, but extracts of protein-chemical conjugates are not commercially available for skin testing. There are limited numbers of *in vitro* tests available for specific IgE to LMW chemical-protein conjugates. Although these tests do not typically have good sensitivity, when positive they can support the diagnosis of OA from a LMW sensitizer.⁴⁹ However, many commercial tests have not been validated with proper homologous controls for these substances.

Work-related changes in physiologic tests

Workplace challenges. Workplace challenge testing involves monitoring patient spirometry at the workplace suspected to cause sensitizer-induced OA. To evaluate baseline variability in FEV₁, a workplace challenge should be preceded by a control day performed away from the suspect workplace. Workplace challenges can be useful when a specific agent cannot be identified as a potential cause for sensitizer-induced OA, there are several potential sensitizers, or a SIC in a controlled setting is not available. Measuring nonspecific airway responsiveness before and after workplace challenges or SIC may reduce the number of false-negative tests by detecting changes in airway responsiveness even without changes in FEV₁.⁵⁸

Induced sputum cell counts. Although not yet widely performed, induced sputum analysis can support the diagnosis of OA before and after workplace challenge, because sputum eosinophils increase after exposure to both HMW agents and some LMW agents. In 1 study of OA from LMW sensitizers, 37% of 38 patients had sputum eosinophil counts of >2.2% while continuing work exposure. High sputum neutrophil counts of >50% occurred in both eosinophilic and noneosinophilic OA groups.⁵⁹ The addition of induced sputum analysis to peak expiratory flow monitoring increases diagnostic specificity.⁶⁰ It has been suggested that induced sputum analysis may assist in the early diagnosis of sensitizer-induced OA, even before development of respiratory symptoms and pulmonary function changes.⁶¹

Exhaled nitric oxide. There have been limited studies examining work-related changes of exhaled nitric oxide (ENO) in patients with OA to sensitizers. Studies have varied, with some finding higher ENO levels in patients with OA and others finding no clear relationship between higher ENO levels and either positive SIC or elevated specific IgE antibody responses.^{2,62}

DIFFERENTIAL DIAGNOSIS

There are a number of diagnoses that may mimic OA, including vocal cord dysfunction, upper respiratory tract irritation, hypersensitivity pneumonitis, rhinosinusitis, and psychogenic factors. Byssinosis, popcorn workers' disease, and flock workers' disease are examples of other occupational lung diseases that may also mimic OA, with the last 2 capable of causing bronchiolitis obliterans. In addition, eosinophilic bronchitis may present with a nonproductive cough, associated with increased eosinophils in

sputum but without evidence of airway obstruction or hyperresponsiveness. Eosinophilic bronchitis has been reported from occupational exposure to a number of agents including latex, acrylates, mushroom spores, and lysozyme.^{2,63}

MANAGEMENT

In OA from sensitizers, complete avoidance of the sensitizer is best from a medical perspective, because better outcomes occur in patients who leave work early in the course of OA versus those who remain at work⁴⁹ (Fig 2). Even when additional medications including anti-inflammatory agents are used, continued exposure after diagnosis is associated with worsening symptoms, lung function, and overall outcomes.^{2,64} When patients are unable or unwilling to change jobs, an alternative approach is to institute exposure reduction by job transfer to low-exposure areas of a company, more vigorous industrial hygiene measures, or use of respiratory protective devices.^{2,65} However, the success of this approach has been demonstrated in only several occupational settings, and in the case of asthma from TDI and some LMW sensitizers, placing workers in environments with lower exposure levels has not been successful at improving outcomes.⁶⁶ Patients with either a confirmed or suspected OA to a sensitizer should receive close medical monitoring if they continue to have workplace exposure.² For OA from certain HMW sensitizers (laboratory animals), allergen immunotherapy may be considered,⁶⁷ although there are little data available about the effectiveness of allergen immunotherapy for OA.

On the basis of limited evidence, expert consensus is that workers with irritant-induced OA might be able to continue in their usual jobs if the risk of a high-level exposure to the inciting agent is reduced by engineering controls and appropriate use of respiratory protective devices.²

However, patients with RADS may have persistent bronchial hyperresponsiveness that makes them subject to exacerbations after exposure to many unrelated workplace irritants and unable to tolerate irritant-prone workplaces.

Patient treatment plans should consider that OA can have a considerable negative economic impact on workers who must leave the workplace and take lower paying jobs or become unemployed, but also to a lesser degree, on workers who stay employed at the same workplace. Accordingly, assisting in worker's compensation determinations, and if need be, serving as an advocate for a worker with OA are important components of patient treatment. The worker's compensation process—often quite litigious in the United States—can be facilitated by obtaining as much objective data as possible.

Management of WEA may require many of the interventions also used for OA, including a need to optimize medical treatment, reduce workplace and nonwork triggers, and determine whether a job change or compensation is appropriate (Fig 2).

PREVENTION AND SURVEILLANCE

A diagnosis of OA in an individual worker showed always be viewed as a potential sentinel health event that may merit workplace evaluation to identify and prevent OA in other workers.²

Prevention of OA is considered to have 3 components^{2,3}:

1. Primary prevention of new OA is directed at reducing workplace exposure to potential causal agents. This may involve reduction of exposure by complete elimination of

a causal agent (eg, through substitution), process modification, respirator use, or engineering control with monitoring of airborne exposure levels.

2. Secondary prevention identifies early evidence of subclinical disease in workers so avoidance actions may be implemented before overt disease develops. This can be accomplished by periodic medical surveillance of workers exposed to potential sensitizers by using tools such as questionnaires, spirometry, and when applicable, immunologic tests.
3. Tertiary prevention attempts to minimize effects of the workplace environment on clinically manifest disease so ongoing exposure does not cause disease progression. This approach involves control of specific factors responsible for disease onset or exacerbation/aggravation, and may involve interventions used for primary and secondary prevention.

There is now a firm evidence basis for the usefulness of prevention measures in reducing onset and progression of OA for many occupational exposures/settings.^{7,68} These include isocyanates, laboratory animal allergens, anhydrides, and latex.^{65,68-71} In 1 study, the use of respiratory protective devices reduced the rate of development of occupational respiratory disease from an acid anhydride from approximately 10% to 2%.⁶⁵

PROGNOSIS AND OUTCOMES

The prognosis of occupational asthma depends primarily on cessation of exposure to the offending agent, the duration of exposure to sensitizers, and the severity of asthma when diagnosed.^{2,7} Timely removal of workers from exposure to a sensitizer causing OA is generally associated with favorable outcomes. Prolonged follow-up may be required to ascertain outcomes in any individual, particularly in OA from sensitizers in which there may be continued improvement of lung function for 2 years or more after exposure ends. In 1 follow-up study of workers with OA to TDI, airway hyperresponsiveness to methacholine persisted in subjects removed from exposure to TDI for more than 10 years, but notably, there was also no plateau of improvement over time.⁷² In another longitudinal study of patients with OA from a variety of sensitizers, the pooled estimate of symptomatic recovery was 32% (range, 0% to 100%) within a median duration of 31 months of follow-up. Overall the pooled prevalence of persistent nonspecific airway hyperreactivity was 73%, but the persistence of hyperreactivity was found to be significantly greater for those with OA from HMW agents compared with those with OA from LMW agents. Consistent with other studies, outcomes were best in those patients with a shorter duration of exposure.⁷³

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Although great strides have been made in understanding OA, there remain many unanswered questions. There are important needs to understand better the pathogenesis of OA from LMW sensitizers, determine circumstances under which irritant asthma might occur when criteria are not met for the long-recognized condition of RADS, and develop improved diagnostic tests to assess sensitization to LMW agents. With the introduction of sputum analysis as a diagnostic tool for OA from suspected sensitizers, further study is needed to determine its usefulness in diagnosing OA from different causal agents. There also is a need to determine better the optimal components of surveillance

programs for prevention of occurrence and progression of OA— with the realization that these components might differ depending on the causal agent and workplace environment. In the United States, greater support is needed for development of centers of excellence that can provide expertise for the evaluation of OA. Despite these unmet needs, research advances in OA now provide a firm evidence basis for many diagnostic and management recommendations that are featured in recently published consensus guidelines on OA.

Clinical implications: This review on OA discusses recent advances in pathogenesis, risk factors, diagnosis, management, and key recommendations from recent consensus guidelines.

REFERENCES

1. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. Environmental and Occupational Health Assembly, American Thoracic Society. American Thoracic Society Statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;167:787-97.
2. Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians consensus statement. *Chest* 2008;134(3 Suppl):1S-41S.
3. Malo JL, Lemi re C, Gautrin D, Labrecque M. Occupational asthma. *Curr Opin Pulm Med* 2004;10:57-61.
4. Boulet LP, Lemi re C, Gautrin D, Cartier A. New insights into occupational asthma. *Curr Opin Allergy Clin Immunol* 2007;7:96-101.
5. Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. *Am J Respir Crit Care Med* 2005;172:280-305.
6. Bardana EJ Jr. Occupational asthma. *J Allergy Clin Immunol* 2008;121:S408-11.
7. Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;62:290-9.
8. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376-84.
9. Banauch GI, Dhala A, Prezant DJ. Pulmonary disease in rescue workers at the World Trade Center site. *Curr Opin Pulm Med* 2005;11:160-8.
10. Andersson E, Olin AC, Hagberg S, Nilsson R, Nilsson T, Toren K. Adult-onset asthma and wheeze among irritant-exposed bleachery workers. *Am J Ind Med* 2003;43:532-8.
11. Quirce S, Gala G, Perez-Camo I, Sanchez-Fernandez C, Pacheco A, Losada E. Irritant-induced asthma: clinical and functional aspects. *J Asthma* 2000;37:267-74.
12. Weichel M, Glaser AG, Ballmer-Weber BK, Schmid-Grendelmeier P, Cramer R. Wheat and maize thioredoxins: a novel cross-reactive cereal allergen family related to baker's asthma. *J Allergy Clin Immunol* 2006;117:676-81.
13. Palacin A, Quirce S, Armentia A, Fernandez-Nieto M, Pacios LF, Asensio T, et al. Wheat lipid transfer protein is a major allergen associated with baker's asthma. *J Allergy Clin Immunol* 2007;120:1132-8.
14. Constantin C, Quirce S, Grote M, Touraev A, Swoboda I, Stoecklinger A, et al. Molecular and immunological characterization of a wheat serine proteinase inhibitor as a novel allergen in baker's asthma. *J Immunol* 2008;180:7451-60.
15. Lemi re C, Chaboillez S, Malo JL, Cartier A. Changes in sputum cell counts after exposure to occupational agents: what do they mean? *J Allergy Clin Immunol* 2001;107:1063-8.
16. Cristaudo A, Sera F, Severino V, DeRocco M, DiLella E, Picardo M. Occupational hypersensitivity to metal salts, including platinum, in the secondary industry. *Allergy* 2005;60:159-64.
17. Patterson R, Zeiss CR, Pruzansky JJ. Immunology and immunopathology of trimellitic anhydride pulmonary reactions. *J Allergy Clin Immunol* 1982;70:19-23.
18. Mapp CE, Boschetto P, Miotto D, De RE. Asthma induced by isocyanates: a model of IgE-independent asthma. *Acta Biomed Ateneo Parmense* 2005;76(Suppl 2):15-9.
19. Wisniewski AV. Developments in laboratory diagnostics for isocyanate asthma. *Curr Opin Allergy Clin Immunol* 2007;7:138-45.
20. Malo JL, L'Archev que J, Lummus Z, Bernstein D. Changes in specific IgE and IgG and monocyte chemoattractant protein-1 in workers with occupational asthma caused by diisocyanates and removed from exposure. *J Allergy Clin Immunol* 2006;118:530-3.
21. Ye YM, Kim CW, Kim HR, Kim HM, Suh CH, Nahm DH, et al. Biophysical determinants of toluene diisocyanate antigenicity associated with exposure and asthma. *J Allergy Clin Immunol* 2006;118:885-91.

22. Campo P, Wisniewski AV, Lumms Z, Cartier A, Malo JL, Boulet LP, et al. Diisocyanate conjugate and immunoassay characteristics influence detection of specific antibodies in HDI-exposed workers. *Clin Exp Allergy* 2007;37:1095-102.
23. Bernstein DI, Cartier A, Cote J, Malo JL, Boulet LP, Wanner M, et al. Diisocyanate antigen-stimulated monocyte chemoattractant protein-1 synthesis has greater test efficiency than specific antibodies for identification of diisocyanate asthma. *Am J Respir Crit Care Med* 2002;166:445-50.
24. Jones MG, Floyd A, Nouri-Aria KT, Jacobson MR, Durham SR, Taylor AN, et al. Is occupational asthma to diisocyanates a non-IgE-mediated disease? *J Allergy Clin Immunol* 2006;117:663-9.
25. Herrick CA, Xu L, Wisniewski AV, Das J, Redlich CA, Bottomly K. A novel mouse model of diisocyanate induced asthma showing allergic-type inflammation in the lung after inhaled antigen challenge. *J Allergy Clin Immunol* 2002;109:873-8.
26. Matheson JM, Johnson VJ, Luster MI. Immune mediators in a murine model for occupational asthma: studies with toluene diisocyanate. *Toxicol Sci* 2005;84:99-109.
27. Park HS, Kim HA, Jung JW, Kim YK, Lee SK, Kim SS, et al. Metalloproteinase-9 is increased after toluene diisocyanate exposure in the induced sputum from patients with toluene diisocyanate-induced asthma. *Clin Exp Allergy* 2003;33:113-8.
28. Lemièrre C, Romeo P, Chabouille S, Tremblay C, Malo JL. Airway inflammation and functional changes after exposure to different concentrations of isocyanates. *J Allergy Clin Immunol* 2002;110:641-6.
29. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:405-13.
30. Gautrin D, Bernstein IL, Brooks SM, Henneberger PK. Reactive airways dysfunction syndrome and irritant-induced asthma. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI, editors. *Asthma in the workplace*. 3rd ed. New York: Taylor & Francis; 2006. p 581-630.
31. Lutz W, Sulkowski WJ. Vagus nerve participates in regulation of the airways: inflammatory response and hyperreactivity induced by occupational asthmagens. *Int J Occup Med Environ Health* 2004;17:417-31.
32. Newman-Taylor A. Asthma and work. *Ann Occup Hyg* 2002;46:563-74.
33. Siracusa A, Marabini A, Folletti I, Moscato G. Smoking and occupational asthma. *Clin Exp Allergy* 2006;36:577-84.
34. Grammer LC, Ditto AM, Tripathi A, Harris KE. Prevalence and onset of rhinitis and conjunctivitis in subjects with occupational asthma caused by trimellitic anhydride. *J Occup Environ Med* 2002;44:1179-81.
35. Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest* 2003;123:283-8.
36. Taylor AJ. HLA phenotype and exposure in development of occupational asthma. *Ann Allergy Asthma Immunol* 2003;90(5 Suppl. 2):24-7.
37. Jeal H, Draper A, Jones M, Harris J, Welsh K, Taylor AN, et al. HLA associations with occupational sensitization to rat lipocalin allergens: a model for other animal allergies? *J Allergy Clin Immunol* 2003;111:795-9.
38. Mapp CE. Genetics and the occupational environment. *Curr Opin Allergy Clin Immunol* 2005;5:113-8.
39. Christiani DC, Mehta AJ, Yu C-L. Genetic susceptibility to occupational exposures. *Occup Environ Med* 2008;65:430-6.
40. Mapp CE, Beghè B, Balboni A, Zamorani G, Padoan M, Jovine L, et al. Association between HLA genes and susceptibility to toluene diisocyanate-induced asthma. *Clin Exp Allergy* 2000;30:651-6.
41. Rihs HP, Barbalho-Kröls T, Huber H, Baur X. No evidence for the influence of HLA class II in alleles in isocyanate-induced asthma. *Am J Ind Med* 1997;32:522-7.
42. Bernstein JA, Munson J, Lumms ZL, Balakrishnan K, Leikauf G. T-cell receptor V beta gene segment expression in diisocyanate-induced occupational asthma. *J Allergy Clin Immunol* 1997;99:245-50.
43. Kim SH, Oh HB, Lee KW, Shin ES, Kim CW, Hong CS, et al. HLA DRB1*15-DPB1*05 haplotype: a susceptible gene marker for isocyanate-induced occupational asthma? *Allergy* 2006;61:891-4.
44. Tarlo SM, Malo JL. ATS/ERS. An ATS/ERS report: 100 key questions and needs in occupational asthma. *Eur Respir J* 2006;27:607-14.
45. Malo JL, Gautrin D. From asthma in the workplace to occupational asthma. *Lancet* 2007;370:295-7.
46. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336-41.
47. Malo JL, Ghezzi H, D'Aquino C, L'Archevêque J, Cartier A, Chan-Yeung M. Natural history of occupational asthma: relevance of type of agent and other factors in the rate of development of symptoms in affected subjects. *J Allergy Clin Immunol* 1992;90:937-44.
48. Malo JL, Ghezzi H, L'Archevêque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991;143:528-32.
49. Beach J, Rowe B, Blitz S, Crumley E, Hooton N, Russell K, et al. Diagnosis and management of work-related asthma. summary, evidence report/technology assessment. Rockville (MD): Agency for Healthcare Research and Quality, Department of Health and Human Services; October 2005. Publication no. 06-E003-1.
50. Vandenplas O, Ghezzi H, Munoz X, Moscato G, Perfetti L, Lemièrre C, et al. What are the questionnaire items most useful in identifying subjects with occupational asthma? *Eur Respir J* 2005;26:1056-63.
51. Bernstein JA. Material safety data sheets: are they reliable in identifying human hazards? *J Allergy Clin Immunol* 2002;110:35-8.
52. Malo JL, Cote J, Cartier A, Boulet LP, L'Archevêque J, Chan-Yeung M. How many times per day should peak expiratory flow rates be assessed when investigating occupational asthma? *Thorax* 1993;48:1211-7.
53. Banks DE, Barkman HW Jr, Butcher BT, Hammad YY, Rando RJ, Glindmeyer HW 3rd, et al. Absence of hyperresponsiveness to methacholine in a worker with methylene diphenyl diisocyanate (MDI)-induced asthma. *Chest* 1986;89:389-93.
54. Enarson DA, Vedral S, Schulzer M, Dybunco A, Chan-Yeung M. Asthma, asthma-like symptoms, chronic bronchitis and the degree of bronchial hyper-responsiveness in epidemiological surveys. *Am Rev Respir Dis* 1987;136:612-7.
55. Chan-Yeung M, Malo JL, Tarlo SM, Bernstein L, Gautrin D, Mapp C, et al. American Thoracic Society. Proceedings of the first Jack Peypys Occupational Asthma Symposium. *Am J Respir Crit Care Med* 2003;167:450-71.
56. Mapp CE, Dal Vecchio L, Boschetto P, De Marzo N, Fabbri LM. Toluene diisocyanate-induced asthma without airway hyperresponsiveness. *Eur J Respir Dis* 1986;68:89-95.
57. Vandenplas O, Binard-Van Cangh F, Brumagne A, Caroyer JM, Thimont J, Sohy C, et al. Occupational asthma in symptomatic workers exposed to natural rubber latex: evaluation of diagnostic procedures. *J Allergy Clin Immunol* 2001;107:542-7.
58. Rioux JP, Malo JL, L'Archevêque J, Rabhi K, Labrecque M. Workplace-specific challenges as a contribution to the diagnosis of occupational asthma. *Eur Respir J* 2008;32:997-1003.
59. Anees W, Huggins V, Pavord ID, Robertson AS, Burge PS. Occupational asthma due to low molecular weight agents: eosinophilic and noneosinophilic variants. *Thorax* 2002;57:231-6.
60. Girard F, Chabouille S, Cartier A, Côté J, Hargreave FE, Labrecque M, et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;170:845-50.
61. Chan-Yeung M, Obata H, Ditttrick M, Chan H, Abboud R. Airway inflammation, exhaled nitric oxide, and severity of asthma in patients with western red cedar asthma. *Am J Respir Crit Care Med* 1999;159:1434-8.
62. Allmers H, Chen Z, Barbinova L, Marczyński B, Kirschmann V, Baur X. Challenge from methacholine, natural rubber latex, or 4,4-diphenylmethane diisocyanate in workers with suspected sensitization affects exhaled nitric oxide (change in exhaled NO levels after allergen challenges). *Int Arch Occup Environ Health* 2000;73:181-6.
63. Quirce S. Eosinophilic bronchitis in the workplace. *Curr Opin Allergy Clin Immunol* 2004;4:87-91.
64. Marabini A, Dimich-Ward H, Kwan SY, Kennedy SM, Waxler-Morrison N, Chan-Yeung M. Clinical and socioeconomic features of subjects with red cedar asthma: a follow-up study. *Chest* 1993;104:821-4.
65. Grammer LC, Harris KE, Yarnold PR. Effect of respiratory protective devices on development of antibody and occupational asthma to an acid anhydride. *Chest* 2002;121:1317-22.
66. Banks DE, Rando RJ, Barkman HW Jr. Persistence of toluene diisocyanate-induced asthma despite negligible workplace exposures. *Chest* 1990;97:121-5.
67. Sastre J, Quirce S. Immunotherapy: an option in the management of occupational asthma? *Curr Opin Allergy Clin Immunol* 2006;6:96-100.
68. Tarlo SM, Liss GM. Prevention of occupational asthma—practical implications for occupational physicians. *Occup Med (Lond)* 2005;55:588-94.
69. Tarlo SM, Liss GM, Yeung KS. Changes in rates and severity of compensation claims for asthma due to diisocyanates: a possible effect of medical surveillance measures. *Occup Environ Med* 2002;59:58-62.
70. Thulin H, Björkdahl M, Karlsson AS, Renström A. Reduction of exposure to laboratory animal allergens in a research laboratory. *Ann Occup Hyg* 2002;46:61-8.
71. Allmers H, Schmengler J, Skudlik C. Primary prevention of natural rubber latex allergy in the German health care system through education and intervention. *J Allergy Clin Immunol* 2002;110:318-23.
72. Padoan M, Pozzato V, Simoni M, Zedda L, Milan G, Bononi I, et al. Long-term follow-up of toluene diisocyanate-induced asthma. *Eur Respir J* 2003;21:637-40.
73. Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman Taylor A, Cullinan P. Outcome of occupational asthma after cessation of exposure: a systematic review. *Thorax* 2007;62:147-52.