

10. Occupational asthma

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A diversity of airborne dusts, gases, fumes, and vapors can induce dose-related respiratory symptoms in individuals exposed in the workplace. These agents can cause annoyance reactions, irritational effects, sensitization, or the induction of corrosive changes in the respiratory tract, depending on their composition, concentration, and duration of exposure. The prevalence of occupational asthma (OA) ranges from 9% to 15% of the asthmatic population. Factors that might influence the development of OA include the work environment, climatic conditions, genetic proclivities, tobacco and recreational drug use, respiratory infection, bronchial hyperresponsiveness, and endotoxin exposure. Pathogenetically, new-onset OA can be allergic or nonallergic in origin. The allergic variants are usually caused by high-molecular-weight allergens, such as grain dust and animal or fish protein. Selected low-molecular-weight agents are also capable of inducing allergic OA. Symptoms ensue after a latent period of months to years. Nonallergic OA can be precipitated by a brief high-level exposure to a potent irritant. Symptoms occur immediately or within a few hours of the exposure. Once the diagnosis of allergic OA is established, the worker should be removed from further exposure in the workplace. In nonallergic OA the worker can return to work if the exposure was clearly a nonrecurring event. If the diagnosis is made in a timely fashion, most workers experience improvement. Prevention is the best therapeutic intervention. (*J Allergy Clin Immunol* 2008;121:S408-11.)

Key words: *Asthma, occupational asthma, reactive airways dysfunction syndrome, endotoxin*

The lungs are the initial target for a diverse spectrum of work-related dusts, gases, fumes, and vapors (Table I). These agents have the capacity to annoy, irritate, sensitize, or induce corrosive changes in the respiratory tract, depending on their physicochemical properties, concentration, and duration of exposure. Occupational asthma (OA) is defined as a condition characterized by reversible obstruction of the airways associated with bronchial hyperresponsiveness (BHR) caused by inhalation of dusts, gases, fumes, or vapors that are produced at or incidentally present at the workplace.¹ It excludes bronchoconstriction caused by exercise or cold air. Preexisting non-OA does not preclude the development of a work-related respiratory disorder. In this instance it

Abbreviations used

BHR: Bronchial hyperresponsiveness
HMW: High molecular weight
LMW: Low molecular weight
OA: Occupational asthma
RADS: Reactive airways dysfunction syndrome

must be determined whether a work exposure caused the preexisting asthma to become transiently symptomatic (reflex bronchoconstriction) or caused an exacerbation of the existing condition by virtue of an intense irritant-induced corrosive effect or the development of a unique sensitization that intensifies the original asthmatic state. In addition, many cases of OA occur in association with chronic bronchitis and emphysema.

PREVALENCE

With few notable exceptions, there are no long-term prospective longitudinal studies of OA. There are a number of retrospective observational studies dealing with specific industries. Nearly all epidemiologic studies have relied on subjective data in identifying asthma. Case definition has been variable in different parts of the world, making it difficult to ascertain whether minimally symptomatic, undiagnosed non-OA was present before the incriminated work-related trigger. Equally problematic is the possibility of preexisting BHR, which might have facilitated the development of overt asthma caused by a viral infection, a nonindustrial allergen, or even a nonspecific environmental pollutant.¹

In 2003, there were an estimated 14 million adults in the United States with asthma.² OA prevalence is said to range between 9% and 15% of the asthmatic population.³ A large population-based study of OA estimated that between 5% and 10% of asthma among adults in European and other industrialized countries was due to work exposures.¹ The actual risk of OA is improved by defining the prevalence among workers within specific industries. OA has been reported in up to 30% of laboratory animal workers, 16% of snow crab processors, 10% of isocyanate workers, and 9% of bakers, particularly in European countries.⁴

Some would argue that the published prevalence rates are an underestimate, citing claims of workers having OA and leaving the industry without formally reporting the disease. This creates a residual resistant "survivor population." Others are said to continue working but remain silent for fear of losing their job or seniority. Still others are said to be given misdiagnoses of non-OA. These scenarios must be counterbalanced with the reality that in the United States workers are protected by unions and state worker's compensation statutes and are unlikely to remain silent with regard to injury. In addition, in an environment in which many workers are uninsured, there is a tendency to invoke the possibility of a work-related injury as a mechanism to cover reimbursement for a needed medical evaluation. Finally, the

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Disclosure of potential conflict of interest: E. J. Bardana has served as an expert witness in civil litigation and worker's compensation independent medical examinations for the states of Alaska, Washington, Idaho, and Montana.

Received for publication May 16, 2007; revised August 3, 2007; accepted for publication August 6, 2007.

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0091-6749/\$34.00

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doi:10.1016/j.jaci.2007.08.005

occasional worker might abuse the worker's compensation system for personal gain.

GENETIC AND OTHER FACTORS

Atopy, asthma, and BHR are determined by multiple interacting genetic and environmental influences.⁵ Atopic individuals are more likely to become sensitized and have OA when exposed to high-molecular-weight (HMW) allergens. The data are less clear with low-molecular-weight (LMW) agents. The incidence of OA associated with exposure to diisocyanates, western red cedar, or the acid anhydrides do not appear to be influenced by the worker's atopic state. An increased incidence of OA in those with atopy is seen with such LMW agents as complex salts of platinum, ethylenediamine, and dimethyl ethanolamine.

Genetic factors can affect the development of OA. Recent observations have shown HLA associations with a specific immunologic response in OA induced by selected LMW agents, including western red cedar, complex platinum salts, trimellitic anhydride, and toluene diisocyanate.⁶ The results of such studies have not always shown consistent associations, and more work is needed to resolve these observations. In addition, industrial pollutants can cause oxidative stress, leading to defects in antioxidant defenses that facilitate the development of asthma. The absence of the M1 polymorphism of glutathione-S-transferase (GSTM1-null genotype) has been associated with an increased risk of isocyanate-induced asthma. It is possible that homozygosity for the GSTP1 valine allele could be a marker of reduced susceptibility for toluene diisocyanate-induced asthma.⁶

In addition to genetic factors, other factors influence the development of OA, including a variety of industrial, climatic, personal, social, and other health factors.⁷ The physicochemical structure and inherent reactivity of chemicals encountered at the workplace are major influencing issues. With relation to the latter, the safety policies enforced in the workplace mitigate the hazards associated with some industrial agents, such as access to material safety data sheets, functional protective equipment, and ideal industrial hygiene practices. In addition, meteorological conditions can modify worker response to a variety of inhalants; for example, diesel exhaust particles have been shown to augment the response to environmental allergens.⁸

The effect of tobacco abuse on the development of OA remains unresolved. A recent review revealed little evidence of an increased risk of OA in active smokers.⁹ However, chronic smoking is associated with a higher incidence of and morbidity from respiratory tract infections. Smoking also adversely enhances airway inflammation and impedes normal healing processes.⁷ There is an additive effect between cannabis and tobacco abuse on adversely affecting the lung.¹⁰

Viral respiratory tract infections are known triggers of asthma and should be considered in the context of any worker presenting with suspected OA.¹¹ In the 1970s, viral infections were believed to trigger about 25% of asthma flares, whereas recent application of PCR techniques detected viruses in 60% to 93% of reported episodes of cough, wheezing, and reduced peak flow.¹² Bacterial infections of the paranasal sinuses are also associated with deterioration of underlying asthma.

BHR is the physiologic hallmark of both OA and non-OA.¹³ Nonspecific BHR is not likely to be a stable continuous state but probably fluctuates over time according to the nature and concentration of environmental pollutants. Although measurement of

TABLE I. Characteristics of industrial allergens and inhalants

Dust	Solids suspended in air • Soybean (farm silos) • Green coffee bean dust (coffee processing) • Latex particles (hospital settings) • Animal protein (animal handlers) • Pollens • Fungal spores (mushroom production)
Gas	Gaseous phase of a liquid or solid - Soluble in water • Ammonia (fertilizer tanks, refrigeration) • Chlorine (water sewage treatment, paper/pulp manufacturer) • Hydrogen sulfide (septic tanks) • Sulfur dioxide (paper mills, refrigerator) • Acrylic aldehyde (plastic/paints) - Insoluble in water • Nitrogen oxides (farm silos, explosives) • Ozone (aircraft cabins) • Phosgene (fires, paint stripping)
Fume	Minute particles from combustion of metals • Aluminum oxide (aluminum plants) • Oxides of cadmium and nickel (mining) • Platinum salts (catalytic converters)
Vapor	Gaseous state of a volatile solid or liquid • Diisocyanates (automotive paints) • Acid anhydrides (adhesives, paints) • Formaldehyde (fires, clothing) • Epoxy amines (paints, plastic manufacture)
Asphyxiants	Simple: interfere with oxygen delivery; chemical: interfere with cell respiration - Simple • Carbon monoxide (vehicle exhaust) • Methane (manure pits) - Chemical • Hydrogen cyanide (burning, plastics) • Hydrogen sulfide (septic tanks) • Methane

BHR provides some insight into variable airflow obstruction, the relationship between BHR and respiratory symptoms is weak. Approximately 50% of subjects with BHR report no symptoms.¹⁴ Although nonspecific BHR is a feature of OA, its presence is not diagnostic of asthma because it is found in a variety of respiratory disorders, including viral respiratory tract infections, current and past tobacco abuse, chronic bronchitis, atopy without asthma, and allergic alveolitis among others. As a result, the positive predictive value of methacholine challenge testing to identify asthma was only 10%, but its negative predictive value was 99%.¹⁴

The complex interaction between endotoxin and allergy is also seen in the occupational literature. Farmers, sawmill workers, and laboratory workers are frequently exposed to endotoxin-rich bioaerosols.¹⁵ Acute endotoxin exposure in occupational settings is linked to a dose-related increase in cough, airway reactivity, and decreases in lung function. With very large exposures, fever and chills and inflammatory changes are seen.¹⁶ Chronic bioaerosol exposure has also linked progressive loss of lung function and development of chronic obstructive pulmonary disease in some. These effects of endotoxin are linked to nonatopic asthma. Recent studies suggest a role for polymorphisms in the CD14 gene in regulating response to endotoxin in occupational settings.¹⁷

Studies of farmers suggest that occupational exposure to endotoxin might protect against the development of atopic asthma in adults.^{16,18,19} However, further confusing our understanding of the effect of endotoxin in asthma are observations that environmental endotoxin augments response to allergen in those already sensitized. Overall, exposure to endotoxin in the workplace appears to be injurious and should be limited. Many have proposed occupational exposure limits for endotoxin.

PATHOGENESIS OF OA

There are 2 basic variants of OA based on pathogenesis: allergic and nonallergic variants. The allergic variant can be further divided into classic IgE-mediated and polyimmunologic forms. The nonallergic variant can be divided into reactive airways dysfunction syndrome (RADS), pharmacologic bronchoconstriction, and reflex bronchospasm.¹

The development of new-onset allergic OA requires a latent period during which sensitization develops (ie, months or years). Exposure usually involves inhalation of soluble HMW proteins, glycoproteins, or other peptide-containing moieties that, in a predisposed worker, result in specific IgE sensitization (Table I). Certain LMW allergens can also cause allergic OA, and examples include salts of platinum, nickel, and chromium. Patients present with the symptoms and signs of classic allergic asthma. Often one sees preceding upper airway and ocular symptoms (rhinoconjunctivitis), followed by work-related airflow obstruction, which tends to intensify during the workweek.²⁰

LMW agents capable of inducing allergic OA act as copolymerizing agents, producing limited immunologic responses. These include complex salts of platinum, nickel, chromium, penicillin, and the epoxy amine compounds.²¹ Another group of LMW agents, including the isocyanates, the acid anhydrides, and plicatic acid, is capable of inducing allergic OA, but the pathogenetic mechanisms are only partially elucidated.^{6,20,22} It is assumed that these inhaled chemicals access viable epithelium and form stable linkages with endogenous protein to acquire immunogenicity. It is possible that glutathione, a ubiquitous intracellular and extracellular transfer agent, plays a role in the transport and binding of reactive chemicals to a variety of biologically important macromolecules.²²

RADS is the best understood variant of nonallergic OA. It results from a high-level workplace exposure to a corrosive irritant, usually a gas (Table I). The onset is abrupt and unassociated with preceding ocular or upper airway symptoms.²³ Many of the agents incriminated in the induction of RADS are gases that are soluble in water. Depending on the corrosive properties of the agent, its concentration, and the duration of exposure, one might have ocular, skin, and mucous membrane burns causing acute inflammatory bronchoconstriction. Commonly implicated agents in the induction of RADS include chlorine dioxide, hydrogen sulfide, anhydrous ammonia, phosphoric acid, toluene diisocyanates, and hydrogen sulfate. The American College of Chest Physicians has published a set of consensus diagnostic criteria that include (1) absence of prior chronic respiratory symptoms; (2) onset of symptoms after a single exposure incident; (3) exposure to a very corrosive agent; (4) onset of symptoms within 24 hours of the exposure with persistence for 3 months; (5) persistence of asthma-like symptoms; (6) presence of airflow obstruction, as determined on the basis of spirometric results, the presence of nonspecific BHR, or both; and (7) exclusion of all other pulmonary disorders.²³

There are only limited pathologic studies related to RADS. They have demonstrated a predominance of lymphocytes in bronchial washings, with evidence of subepithelial thickening and fibrosis. The process is postulated to be the result of extensive denudation of bronchial epithelium, resulting in inflammation and release of proinflammatory chemotactic and toxic mediators.²³

DIAGNOSIS AND TREATMENT

The medical history is a key element in the initial evaluation of OA. The history should elicit the features of a work-related airway disease and provide clues to the linkage to 1 or more suspect work exposures. As expected, the history has a high degree of sensitivity (87%) but a low specificity (22%) for the diagnosis of OA.²⁴ Patient recall of past symptoms, illnesses, and medical care is often unreliable and inconsistent. The physical examination should be carried out to accurately record the presence of ocular, nasal, sinus, oropharyngeal, and pulmonary abnormalities.

Reviewing past medical and employment records can enhance the diagnostic process by accessing information for which the worker might have no awareness or recollection and corroborating important historical benchmarks. In reaching a final diagnosis of OA, the history alone has been found to be unacceptable.

The use of immunologic testing in the diagnosis of allergic OA is limited. The presence of allergen-specific IgE antibodies might assist in the diagnosis of OA caused by HMW allergens. However, data derived solely from cutaneous or serologic studies should not be used to conclude that a suspect allergen was the sole cause of the OA.²⁵ Radiologic observations have their principal utility in either excluding or implicating alternative conditions in the differential diagnostic process. The availability of high-resolution computed tomography has been helpful in assessing the extent of coexisting emphysema or uncovering the presence of fibrosis, bronchiectasis, or other processes that might explain the presenting symptoms.

Pulmonary function studies are indispensable in the diagnosis and assessment of the severity of OA. Most importantly, there should be no doubt that reversible airflow obstruction exists. If the results of spirometric analysis are normal, methacholine challenge can be used to demonstrate nonspecific BHR. It is essential that pulmonary function studies be carried out according to American Thoracic Society criteria and that positive responses to methacholine provocation at concentrations of 8 mg/mL or greater be interpreted cautiously.¹ As new observations regarding its validity develop, exhaled nitric oxide might eventually replace methacholine provocation as a safe and rapid diagnostic tool for OA.^{26,27}

The suspected temporal adverse effect of an industrial agent can be initially explored by comparing peak expiratory flow rates during a period of work abstinence and after a return to work. Data from such observations should be interpreted cautiously because the maneuver is effort dependent and can be relied on only when executed under direct observation with published guidelines. Comparison of nonspecific BHR after a period of continuous occupational exposure with a baseline after a 3- to 4-week period of total abstinence from exposure to the suspect agent would be much more reliable. Provided there are no changes in medication, an increase in bronchial reactivity of more than 2 doubling concentrations (or doses) would be considered significant. The same process could use a 20% increase in exhaled nitric oxide at a flow rate of 250 mL as significant. There are as yet no studies in

the occupational setting to verify the latter, but they are likely to be studied in the future. Lastly, one could use cross-shift spirometric data (ie, preshift and postshift spirometry over the course of an entire 1 or 2 workweeks). The gold standard for diagnosis of OA is achieved only by using a controlled bronchial challenge with subirritant concentrations of the suspected allergen. Such a test is invasive, time consuming, and definitely poses some risk to the worker and therefore must be performed with appropriate informed consent.

PREVENTION, MANAGEMENT, AND DIAGNOSIS

Adoption and enforcement of optimum industrial hygiene measures in the workplace is the only effective means to reduce or completely eliminate ambient levels of known allergens or respiratory irritants. Employers must mandate that employees use properly fit-tested and approved respirators where appropriate (spray painters using catalyzed paints) and install effective exhaust systems or develop enclosed, automated robotic processes. Management of OA is identical to that of non-OA, with the caveat that the patient must be removed from any further exposure to the causative agent in a timely manner. The major prognostic indicators for OA include the total duration of exposure to the causative agent, asthma severity at the time of diagnosis, and the pathogenic mechanisms operative in the original induction of OA.²⁸ The majority of individuals who have OA and receive diagnoses in a timely fashion and are removed from further exposure achieve good control of their asthma and are capable of resuming full employment in an alternative job. On the other hand, where the diagnosis of OA is delayed or where the worker refuses to comply with warnings regarding avoidance, chronic asthma symptoms can be expected to persist with resultant deterioration, which might become irreversible.

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Occupational asthma

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Learning objectives: "Occupational asthma"

1. To understand the definition and classification of new-onset occupational asthma.
 2. To summarize the various factors that may influence the development of occupational asthma.
 3. To identify valid approaches to the diagnosis of occupational asthma.
-

CME items

Question 1. Which of the following chemicals has never been reported to cause reactive airways dysfunction syndrome?

- A. anhydrous ammonia
- B. chlorine gas
- C. carbon dioxide
- D. phosgene

Question 2. The prevalence of occupational asthma is estimated to be what percent of the asthmatic population?

- A. 1% to 3%
- B. 2% to 5%
- C. 9% to 15%
- D. 30% to 40%

Question 3. Which of the following industrial gases is soluble and likely to cause ocular and upper airway inflammation?

- A. ozone
- B. nitrogen dioxide
- C. hydrogen sulfide
- D. phosgene

Question 4. Which of the following is linked to acute high-level endotoxin exposure in occupational settings?

- A. fever and chills
- B. loss of allergy skin test reactivity
- C. increased likelihood of pneumonia
- D. increased likelihood of being sensitized to toluene diisocyanate