

8. Occupational asthma and allergies

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A diversity of airborne dusts, gases, fumes, and vapors can cause dose-related symptoms in individuals exposed in the workplace. More than 250 chemicals have been incriminated as a cause of occupational asthma (OA). The prevalence of OA ranges from 2% to 6% of the asthmatic population. Predisposing factors facilitating the development of OA include the work environment, climatic conditions, genetic proclivities, tobacco and recreational drug use, respiratory infection, and bronchial hyperresponsiveness. Pathogenetically, new-onset OA may be immunologic or nonimmunologic in origin. The immunologic variants are usually caused by high molecular-weight allergens such as grain dust and animal or fish protein. Symptoms ensue after a latent period of months to years. Nonimmunologic 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. In either instance, once the diagnosis is established, the worker should be removed from the workplace. If the diagnosis is made in a timely fashion, most workers experience improvement. Prevention is the best therapeutic intervention. (*J Allergy Clin Immunol* 2003;111:S530-9.)

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

After the skin, the respiratory tract is the most commonly affected organ in the workplace.¹ It is the point of entry for a diversity of airborne dusts, gases, fumes, and vapors that may cause dose-related symptoms in exposed workers. At one end of the spectrum, transient annoyance reactions may occur with low concentrations of mild irritants or disagreeable odors. Irritation of the respiratory mucosa occurs when modest concentrations of soluble inhalants are encountered. Alternatively, there are corrosive chemicals capable of causing skin burns, ocular damage, and acute inflammatory changes of the nasopharynx, larynx, and bronchi. Lastly, there are industrial agents capable of inducing sensitization.² Numerous chemicals and organic dusts have been implicated as potential causes of new-onset occupational asthma (OA), rhinitis, and other hypersensitivity lung disorders.

DEFINITIONS

OA is characterized by variable airway obstruction associated with bronchial hyperresponsiveness (BHR). It is caused by bronchial inflammation secondary to inhalation of ambient dusts, gases, fumes, or vapors that are

Abbreviations used

ATS:	American Thoracic Society
BHR:	Bronchial hyperresponsiveness
HMW:	High-molecular weight
LMW:	Low-molecular weight
OA:	Occupational asthma
RADS:	Reactive airways dysfunction syndrome

produced at, or incidentally present at the workplace.³ OA may also be defined as variable airflow limitation caused by a specific agent in the workplace.⁴ The definition of OA assumes significant legal importance in the context of different state workers' compensation statutes.^{5,6} Preexisting asthma does not preclude development of a work-induced respiratory disorder. However, the clinician must determine whether the putative work exposure caused the preexisting asthma to become transiently symptomatic, or caused a permanent worsening of preexisting asthma by virtue of either an intense corrosive effect or a unique sensitization that worsened the preexistent asthma.

EPIDEMIOLOGY

Despite significant advances in the past several decades, there is a paucity of reliable data on the prevalence of occupational lung disorders. Much of what has been published represents anecdotal case reports, descriptions of small clusters of cases, or retrospective prevalence studies with notable exceptions.^{7,8} There are essentially no long-term, prospective, longitudinal studies. In addition, nearly all epidemiological studies have relied on subjective data in identifying bronchial asthma. Case definition has been variable in different parts of the world. In most instances, it is not possible to ascertain whether minimally symptomatic, undiagnosed, non-OA was present prior to any suspected work exposure. Equally problematic is whether preexisting, unrecognized, asymptomatic BHR predisposed to the development of adult-onset asthma secondary to a viral respiratory infection, exposure to a nonoccupational allergen, a pharmacologic agent, or a nonspecific airborne irritant such as sulfur dioxide or ozone. Many patients report having childhood asthma that abated in late adolescence. Recent observations indicate that asymptomatic BHR persists through adolescent and young adult life and cannot be modified by inhaled corticosteroids.⁹ It is not known whether BHR predisposes to the later development of OA, although some consider it an acquired phenomenon rather than a predisposing factor.¹⁰ As well, a number of individuals are underdiagnosed in adolescence, but later found to have asthma.¹¹

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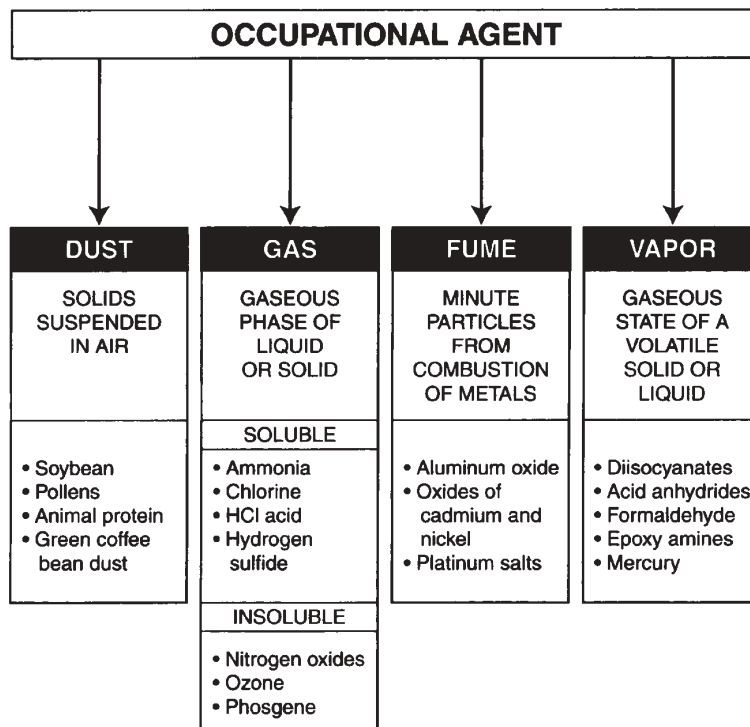


FIG 1. Characteristics of inhaled industrial agents. Dependent on their biochemical characteristics, concentration, and exposure duration, these agents can cause a continuum of symptoms starting with annoyance, irritation, or corrosion. Certain dusts and vapors have the capacity to sensitize (Adapted⁴⁸ with permission). *HCl*, Hydrochloric (acid).

An estimated 18 million people in the United States have asthma.^{12,13} OA prevalence is said to range between 2% and 6% of the asthmatic population.¹⁴ Consistent with this estimate, a recent large population-based study of OA estimated that between 5% and 10% of cases of asthma among adults in European and other industrialized countries were secondary to occupational exposures.¹⁵ Unfortunately, the latter study did not distinguish between new-onset OA and preexisting asthma that was aggravated due to a subsequent work exposure.

The older literature reports prevalence rates of 20% or more in certain industries. Many of these observations occurred before modern industrial hygiene practices were imposed and no longer apply to modernized manufacturing facilities with enforced safety policies. As well, there are marked differences in potential exposures for the same industry in different parts of the world. Family-run bakeries in Europe have vastly different airborne flour-dust exposure than large bread-production facilities in the United States.

Many investigators believe that the 5% prevalence for OA represents an underestimate. There are claims of some workers developing OA who leave without reporting the illness, creating a residual "survivor population." Others argue that some workers remain on the job with OA and neglect to report it for fear of losing their job or their seniority. Others with OA are said to be misdiagnosed with non-OA. These scenarios must be balanced with the reality that in a setting where workers are pro-

tected by unions and state workers' compensation statutes, it is highly improbable that any worker would remain silent with even the mere suggestion of an industrial injury. In addition, in a population where some 40 million remain uninsured and even more underinsured, there is a tendency to invoke the possibility of an occupational illness or injury as mechanism of reimbursement. Lastly, there is the occasional worker who abuses the system for personal gain.

PREDISPOSING FACTORS

The development of OA is influenced by a variety of industrial, climatic, genetic, social, and medical factors.

Workplace factors

A worker's response to an industrial exposure depends on the physicochemical nature of the agent (Fig 1), and employer policies and attitudes on worker-safety programs. This includes easy access to material safety data sheets, availability of functional protective equipment, training in the use and care of the safety equipment (eg, respirator clearance spirometry, fit testing), enforcement and adherence to safety policies, and implementation of effective industrial hygiene measures.¹⁶

Climatic conditions

Meteorological conditions may modify worker response to an inhaled antigen or irritant. Prevailing

TABLE I. Selected asthmogenic agents categorized by molecular weight

HMW	LMW
Insect parts	Penicillins
Mammalian proteins	Cephalosporins
Avian proteins	Sulfonamides
Fish-derived allergens	Platinum salts
Seeds (linseed, flaxseed)	Nickel
Grain dust	Vanadium
Green coffee bean dust	Diisocyanates
Castor bean dust	Acid anhydrides
Natural rubber latex	Epoxy amine compounds
Vegetable gums	Reactive azo dyes
Psyllium	Colophony
Enzymes	Western red cedar (plicatic acid)

winds determine the direction of an irritating stack emission. Several asthma epidemics in Barcelona, Spain between 1981 and 1987 were attributed to large amounts of soybean dust released into the atmosphere.¹⁷ The presence of seasonal allergens or environmental pollutants (eg, diesel exhaust particles) may augment the response to work-related allergens.¹⁸

Genetic influences

The development of atopy, asthma, and BHR are determined by multiple and interacting genetic and environmental influences.¹⁹ Atopic individuals are more likely to develop OA when exposed to high molecular-weight (HMW) allergens and selected low molecular-weight (LMW) agents mediated by the T helper type 2 cytokine IgE cascade (Table I). Development of OA and sensitization to LMW agents is influenced by human leukocyte antigen polymorphisms.²⁰ This has been convincingly demonstrated with respect to sensitization to complex platinum salts, trimellitic anhydride, and toluene diisocyanate.²⁰⁻²²

Tobacco and recreational drug use

There are still some 50 million smokers in the United States and an even higher prevalence in other parts of the world.²³⁻²⁵ Smoking is a potential predisposing and aggravating factor in the development of OA.^{26,27} Several industrial studies of IgE-related allergy have shown the risk for smokers to be 4 to 6 times higher than that for nonsmokers.^{17,28,29} There also is an association between chronic cigarette smoking and a higher incidence of and morbidity from respiratory tract infections.³⁰ Cannabis is used by a substantial minority of young adults, even though its use is prohibited by law.³¹ Chronic cannabis smoking is associated with increased symptoms of chronic bronchitis and decreased lung function. There also is an additive effect between cannabis and tobacco abuse.^{32,33}

Respiratory infection

Viral infections are recognized as an important trigger of asthma exacerbations.³⁴ This must always be considered in the context of any worker presenting with sus-

pected OA. Insights into the mechanisms of viral-induced asthma have been notably enhanced by the use of molecular detection techniques, ie, polymerase chain reactions. In the late 1970s, viral infections were believed to be operative in triggering 25% of asthma exacerbations,³⁵ whereas recent application of polymerase chain reactions detected viruses in 85% of reported episodes of cough, wheezing, and reduced peak flow.^{36,37} A recent study observed that wheezing in an asthmatic following rhinovirus exposure can be triggered in the absence of any overt symptoms or signs of a viral coryza.³⁴ Bacterial infections of the paranasal sinuses are also associated with deterioration of underlying asthma.³⁸ Infections with *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been associated with flares of asthma.^{39,40}

BHR

BHR is regarded as the physiologic hallmark of both OA and non-OA.⁴¹ BHR represents a common physiological pathway of several mechanisms leading to a lowered threshold of airway narrowing to bronchoconstrictor stimuli. BHR reflects and is likely partially caused by airway inflammation. Although the measurement of BHR provides quantitative insight in variable airflow obstruction, the relationship between BHR and respiratory symptoms is weak. Approximately 50% of subjects with BHR report no respiratory symptoms.⁴² BHR follows a normal distribution in the general population with approximately 20% of individuals without evidence of asthma or other respiratory disease having mild BHR.⁴³

The diagnostic implications of a positive methacholine challenge test in the setting of presumptive OA continue to confuse and occasionally mislead many clinicians. Although BHR is a feature of OA, it is not a diagnostic test. BHR is associated with a variety of other respiratory disorders including viral respiratory infections, chronic tobacco abuse, chronic bronchitis, allergic rhinitis without asthma, and hypersensitivity pneumonitis.^{2,44} The positive predictive value of a positive methacholine challenge to determine the presence of asthma is only about 10%, whereas its negative predictive value is about 99%.⁴⁵

Miscellaneous factors

Diagnostic considerations that could be confused with OA include aspirin-induced asthma, gastroesophageal reflux, and a variety of pharmaceutical agents that are known to have an adverse impact on the course of asthma, eg, β -adrenergic blocking agents and angiotensin-converting enzyme inhibitors.

CLINICAL AND PATHOGENIC FEATURES

From a clinical and pathologic perspective, new-onset OA can be divided into immunologic and nonimmunologic variants. The immunologic variant can be further divided into classic IgE-mediated and polyimmunologic variants. The nonimmunologic variant can be divided into reactive airways dysfunction syndrome (RADS),

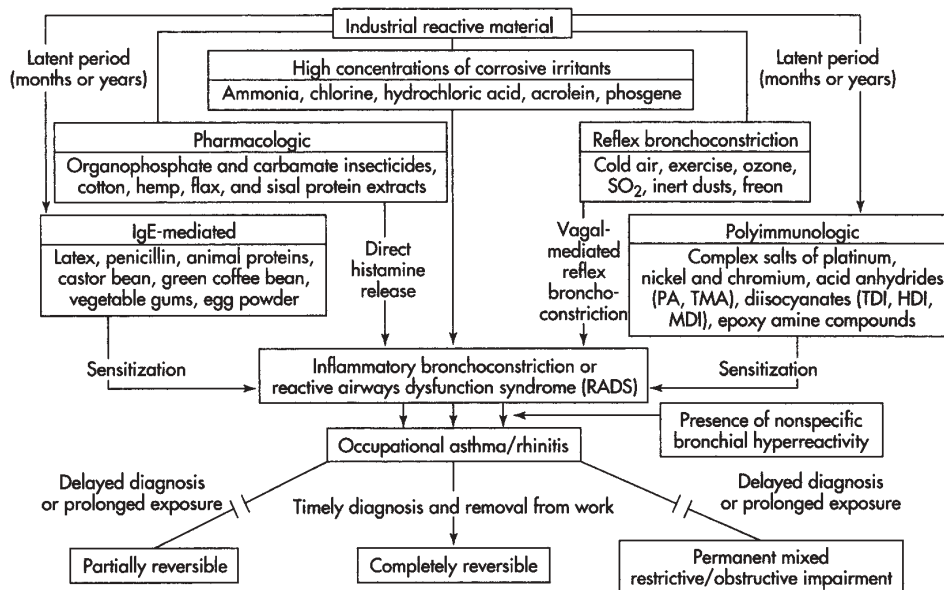


FIG 2. Schematic conceptualization of several pathogenetic mechanisms of occupationally induced airway obstruction (Adapted⁴⁸ with permission). PA, Phthalic anhydride; TMA, trimellitic anhydride; TDI, toluene diisocyanate; HDI, hexamethylene diisocyanate; MDI, methylene diphenyl diisocyanate.

reflex bronchoconstriction, and pharmacologic bronchoconstriction (Fig 2). These considerations allow us to partially comprehend why acute, high-level exposures to selected industrial irritants such as toluene diisocyanate might provoke acute inflammatory bronchoconstriction in one instance, whereas chronic low-level exposures may induce an immunologic or pharmacologic OA in another instance (Fig 2).^{46,47}

ALLERGIC OA

New onset, allergic OA can be triggered by a large number of HMW allergens, predominantly proteins derived from animals, plants, foods, and enzymes (Table I).⁴⁸ In the majority of cases, OA induced by these agents is associated with evidence of a specific T helper type 2 lymphocyte response and specific IgE antibody. The initial step in the induction of an allergic reaction is the interaction of specific work-related allergens with IgE-sensitized mast cells, basophils, and other cells in airway tissue. IgE-sensitized mast cells secrete and generate bioactive mediators that facilitate the development of allergic inflammation. There are a group of LMW agents including isocyanates, the acid anhydrides, and plicatic acid that are capable of inducing OA, but the pathogenesis remains only partially elucidated.⁴⁷ Specific IgE and IgG antibodies are found in only a minority of cases and their precise role is unclear.⁴⁹ Bronchial biopsy specimens show significant numbers of activated T lymphocytes proximal to the bronchi suggesting they play an active role in eliciting allergic inflammation. The majority of these cells are of the CD8 phenotype capable of producing interferon- γ and IL-5, but little IL-4.^{50,51} Studies have shown that T lymphocytes also play an active

role in the induction of OA, ie, the mechanism is poly-immunologic.⁵² Recent evidence implicates reactive chemical adduction of epithelial cell proteins and other intracellular/extracellular moieties.⁵³ It is possible that glutathione, a ubiquitous intracellular and extracellular transfer agent, plays a role in the transport and adduction of reactive chemicals to a variety of biologically important macromolecules.⁵⁴ There remains a number of industrial agents for which the pathogenesis remains largely elusive. The 2 largest groups of chemicals in this category include certain wood dusts and a variety of copolymerizing compounds or hardening agents used in the manufacture of resins or plastics (Table I). The development of murine models with characteristics of human disease may facilitate a better understanding of the immunopathogenesis of OA induced by these agents.⁵⁵

The clinical presentation of the typical patient with new-onset allergic OA frequently parallels the symptoms of patients with classic allergic disorders. After a latent period of months or years, many develop upper-airway and ocular symptoms of occupational rhinitis.^{48,49} Subsequently, they develop lower respiratory symptoms. Work-related airflow obstruction, characterized by chest tightness, cough, and dyspnea, occurs that often intensifies during work. Onset of symptoms may be immediate, delayed, or biphasic (dual), consistent with the early- and late-phase allergic response.

NONALLERGIC OA

Nonallergic OA usually results from a high-level exposure to a potent respiratory irritant in the workplace (Table II). Contrary to allergic OA, the onset is abrupt without a latent period. The clinical sequelae of any acute exposure

TABLE II. Industrial agents frequently incriminated in causation of RADS

Chlorine	Phosphoric acid
Toluene diisocyanate	Hydrochloric acid
Phosgene	Hydrogen sulfate
Sulfuric acid	Anhydrous ammonia
Smoke inhalation	Diethylene diamine

TABLE III. Proposed criteria for the diagnosis of RADS

Major criteria (as proposed by the American College of Chest Physicians) ⁶³
Absence of previous respiratory complaints
Onset of symptoms after a single exposure incident
Exposure to an extremely high concentration of an irritating industrial agent
Onset of symptoms within 24 h after exposure, with persistence of symptoms for at least 3 mo
Symptoms simulating asthma
Presence of airflow obstruction on pulmonary function testing and/or presence of nonspecific BHR
All other respiratory disorders excluded
Minor criteria ⁶⁴
Absence of an atopic state
Absence of peripheral and pulmonary eosinophilia
Absence of cigarette smoking for 10 years
BHR with a PC ₂₀ at or below 8 mg/mL of methacholine
Histopathology and/or bronchoalveolar lavage showing minimal lymphocytic inflammation

PC, Provocative concentration.

depends on the physiochemical properties of the dust, gas, fume, or vapor involved (Fig 1), as well as intrinsic host factors. Highly soluble gases are likely to cause pharyngeal and laryngeal injury associated with laryngeal edema.⁵⁶ Such exposures are usually associated with skin irritation, conjunctivitis, nasal erythema, and, if severe, mucosal ulceration with edema. Soluble gases are significantly absorbed by the mucous membranes of the upper airways, minimizing lower-airway damage. The latter depends on the nature and extent of the exposure and whether the worker is exercising and mouth breathing, as opposed to resting and nasal breathing. In contrast, the insoluble gases cause little or no upper-airway irritation or tissue damage and are much more likely to precipitate intense pulmonary edema, bronchiolitis, and alveolitis after a variable period of time.⁵⁶

There are several variants of nonallergic OA, but by far the most common was originally described by Gandevia⁵⁷ in 1970 and referred to as "acute inflammatory bronchoconstriction." Onset of asthma followed an acute, accidental exposure to high concentrations of a potent irritant, eg, chlorine, hydrogen sulfide, and phosgene. Airflow obstruction developed within hours of the exposure secondary to a chemically induced bronchitis or

bronchopneumonia. Symptoms usually peaked within a week and started to regress over the next several months.^{58,59} Many afflicted workers continued to manifest chronic asthma or asymptomatic BHR, dependent on the corrosive properties of the trigger.

In 1981, Brooks and Lockey⁶⁰ coined the term "RADS" to describe 13 workers acutely exposed to respiratory irritants. In the ensuing years, RADS replaced "inflammatory bronchoconstriction" and has become the accepted terminology for this process. The diagnosis of RADS requires the presumption of preexisting normal pulmonary physiology and the absence of BHR. This presumption is the obvious weakness in establishing this diagnosis and has since precipitated much discussion. Several versions of diagnostic criteria have been published.⁶¹⁻⁶³ Alberts and dePico⁶³ critically analyzed the RADS literature and presented their rationale for relying on the American College of Chest Physicians Consensus Criteria outlined in Table III. The author has proposed that these criteria be categorized as "major criteria." Because past and current cigarette smoking and atopy are independently associated with BHR (the only objective criterion), 5 "minor criteria" have been proposed that would strengthen the diagnosis considerably if at least 4 were met (Table III).⁶⁴ There is growing support for the utilization of an 8-mg/mL concentration of methacholine as the upper limit for a positive test.^{65,66}

The pathogenesis of RADS is postulated to be the result of extensive denudation of the bronchial epithelium that results in airway inflammation.^{67,68} This denudation activates nonadrenergic, noncholinergic pathways via axon reflexes with development of neurogenic inflammation. Nonspecific macrophage activation and mast cell degranulation result in the release of proinflammatory chemotactic and toxic mediators. A limited number of bronchial biopsies show replacement of epithelium by a fibrinohemorrhagic exudate. There is subsequent desquamation of epithelium with a lymphocytic exudate that can persist for months.^{67,68}

Nonallergic OA may also be triggered by agents producing a direct pharmacologic action on the respiratory mucosa (Fig 2), eg, organophosphate and carbamate insecticides. In sufficient doses, these agents inhibit acetylcholinesterase, which potentiates the effect of acetylcholine released from vagal fibers innervating bronchial smooth muscles and producing transient bronchoconstriction.

Reflex bronchoconstriction is the third variant of nonallergic OA. It is distinguished from RADS by the intensity and nature of the exposure, ie, chronic, low to moderate-dose, irritant-induced OA. Certain chemicals and inert gases are thought to have the capacity to cause reflex bronchospasm by disrupting the delicate balance of adrenergic control involved in maintaining bronchial tone. However, it is unlikely that this mechanism can induce new-onset OA. It is more likely to be operative in patients with preexistent subclinical asthma, asymptomatic BHR, or atopy. Brooks et al^{66,69} recently studied such a group and came to similar conclusions.

MATERIAL SAFETY DATA SHEET		
I PRODUCT IDENTIFICATION		
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO	
ADDRESS		
TRADE NAME		
SYNONYMS		
II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT		HAZARD DATA
III PHYSICAL DATA		
BOILING POINT 760 MM HG		MELTING POINT
SPECIFIC GRAVITY (H ₂ O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H ₂ O % BY WT
% VOLATILES BY VOL		EVAPORATION RATE IBUTYL ACETATE II
APPEARANCE AND ODOR		

FIG 3. Format of a material safety data sheet. (Reproduced⁷⁵ with permission).

DIFFERENTIAL DIAGNOSIS

In evaluating patients with suspected OA, it is important to understand the diagnostic criteria that distinguish it from a variety of closely related conditions. The most important initial step is to establish that asthma truly exists, ie, there must be a reliable demonstration of variable airflow obstruction by reliable physiologic testing.⁶⁵ Asthma is not infrequently misdiagnosed even in the setting of a tertiary care asthma center.⁷⁰ Second, since OA is linked to causes and conditions attributable to a particular work environment, the examiner must exclude the possibility that the asthma is due to triggers of a nonoccupational nature. Challenging in this respect is the atopic worker with preexisting allergic rhinitis in whom subclinical asthma may have been present, but undiagnosed until an industrial incident focused attention on the lower airways. Although there is a widely held belief that children with asthma "outgrow" their disease, recent observations revealed pulmonary function abnormalities and BHR in such patients.^{11,71,72} Transient exacerbation of preexisting subclinical asthma by irritant triggers at the workplace is a common occurrence in the differential diagnosis of "new-onset" OA. In the latter case, there may be some transient symptoms without permanent worsening of underlying bronchial inflammation and/or

BHR.⁷³ Thirdly, other variants of asthma such as allergic bronchopulmonary aspergillosis, aspirin-sensitivity syndrome, and Churg-Strauss allergic granulomatosis must be ruled out. Finally, unrelated disorders masquerading as asthma must be excluded, eg, industrial bronchitis, congestive heart failure, vocal cord dysfunction, and hypersensitivity pneumonitis.

DIAGNOSIS

History and physical examination

The medical history is a key element in the evaluation of OA. It provides the examiner with clinical features of work-related airway disease and assists in confirming the linkage to one or more likely work exposures. Rhinitis may precede development of lower-airway symptoms or may parallel asthmatic symptoms especially when HMW antigens are causal.⁷⁴ Many patients have symptoms on a continuous basis triggered by other coincidental nonoccupational triggers or as a result of late-phase immunologic responses to occupational allergens.

Because of time limitations, a questionnaire may be helpful as a tool to amplify the interview process.⁷⁵ The history should include a chronology of symptom onset in

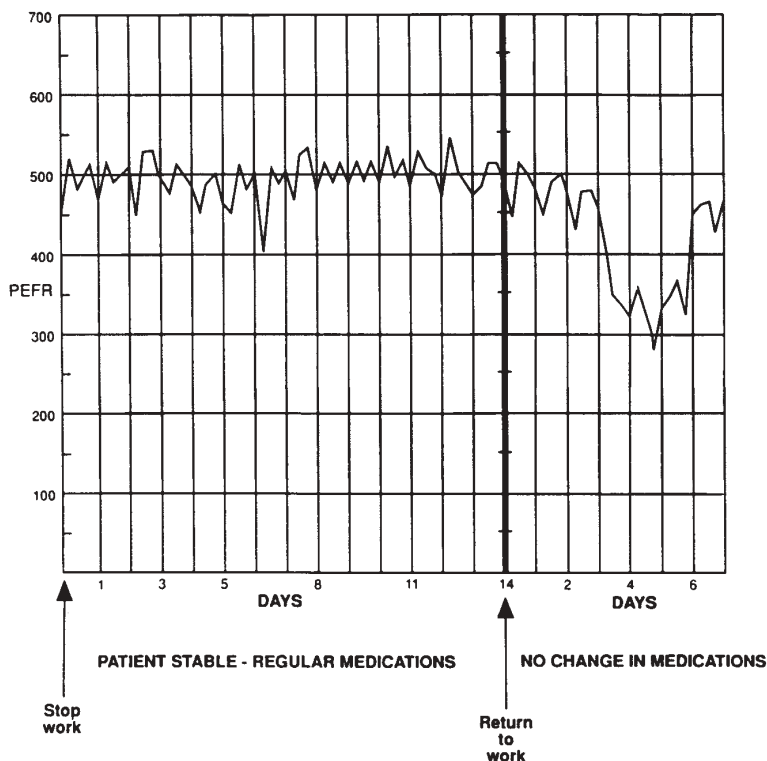


FIG 4. Schematic representation of serial PEFR charted during a period of work abstinence and after return to work. Peak flow is seen to drop by 40% by the fourth day of work (Adapted⁴⁸ with permission).

relation to any suspect work exposures. The history should reflect all prior employers and their work exposures with a detailed understanding of the protective equipment used by the worker, ie, its initiation and adherence. The worker should provide material safety data sheets on all relevant exposures (Fig 3). The evaluator should review all prior medical records to verify key points in the medical history and uncover information the worker may have forgotten. However, diagnosing OA based on the history alone is totally unacceptable.⁴⁹ Though the history has been found to have a high degree of sensitivity, ie, 87%, it has a low specificity (22%) for the diagnosis of OA.^{76,77} Recall of past symptoms, illnesses, and medical care is often unreliable and inconsistent.⁷⁸

The physical examination should be carefully conducted to record the presence of ocular, nasal, oropharyngeal, and pulmonary abnormalities. It is not unusual for a patient with new-onset OA to have a normal examination. In those instances where the medical history is compelling, but the examination is normal, and reversible airways obstruction is not apparent on spirometry, an assessment of BHR can be useful.

Establishment of a cause-and-effect relationship

It is critical to confirm OA by means of objective testing. This can be done in a sequential fashion starting with uncomplicated procedures and progressing to more sophisticated testing as suspicions are confirmed.

Pulmonary function studies

Pulmonary function tests are essential both in the diagnosis and assessment of severity of OA. Diagnosis of OA demands an unequivocal demonstration of reversible airflow obstruction.^{65,70} The American Thoracic Society (ATS) criteria demand a minimum of a 12% increase in forced expiratory volume in 1 second with bronchodilator. When assessing spirometric data from primary care providers, the evaluator must recognize possible inadequacies in the data, ie, less than 20% of spirometry tests performed at primary care practices met ATS criteria.⁷⁹

A provisional cause-and-effect relationship to a workplace agent can be developed by serial determination of PEFR during a period of work abstinence followed by a return to work (Fig 4). Such testing has to be interpreted with caution, because the maneuver is effort-dependent and requires the cooperation of the worker. Where malingering may be an issue, dependable data may be elusive, ie, 2 studies using a hidden computer chip to store PEFR data demonstrated that approximately 50% of values were inaccurately reported on diaries.^{80,81}

A more secure diagnostic approach assesses the degree of BHR before and after return to work after a period of 3 to 4 weeks off work. Providing there are no significant medication changes or respiratory infection, a change in BHR greater than 2 doubling concentrations (or doses) is considered significant.^{75,82}

A third approach relies on cross-shift spirometric measurements. Performing spirometry to compare prework- and postwork-shift forced expiratory volume in 1 second daily for at least a week has been used to detect work-related pulmonary function-test deterioration.⁸² In essence, this represents a "work provocation challenge."

Bronchial provocation studies

These tests are still considered the gold standard to confirm the diagnosis of OA.^{2,49,75,82-85} There are 2 approaches to bronchial provocation with suspected industrial sensitizers. The initial methods were designed to recreate the workplace and the suspected agent, ie, "simulated work provocation." These pragmatic tests were performed with chemical dusts, wood dusts, flour, paint vapors, etc. Controls using lactose powder were fashioned, and despite the imprecision of actual challenge concentrations, impressive and reproducible data were obtained.⁸⁶ Recently, provocation tests have been limited to specialized centers with highly trained personnel.^{10,82} Several protocols are available using controlled bronchial challenge with subirritant concentrations of the suspected immunogen.⁸⁷ These tests pose some risk and require appropriate informed consent for the procedure. The patient may require admission to hospital for close surveillance.⁸²

Immunologic testing

The application of immunologic testing in the diagnosis of allergic OA is limited. The demonstration of cutaneous reactivity, or presence of specific IgG- or IgE-specific *in vitro* antibodies reflect exposure and sensitization, but do not implicate a specific target organ. Demonstration of IgE may be quite helpful in the case of HMW antigens, eg, animal protein, snow crab, psyllium. A negative test does not necessarily exclude the diagnosis, but it does make it less likely. However, the presence of serum or skin-sensitizing antibody alone cannot be equated to the presence of a "symptomatic state." The clinician must differentiate the state of subclinical "sensitization" from an "allergic symptom complex."⁸⁸

PREVENTION AND MANAGEMENT

The most effective manner of preventing OA is to insulate at-risk workers from potentially hazardous agents. This requires the employer to adapt and enforce optimum industrial hygiene measures that will reduce or eliminate ambient levels of known irritants and immunogens. This can be accomplished by utilization of approved respirators that have been properly fit tested, by highly effective exhaust devices, or by installation of an enclosed automated process such as robotics. Many employers conduct surveillance of their industrial processes, ie, regularly measure ambient levels of potentially harmful chemicals, and have mandatory programs to monitor the respiratory health of employees, which include annual spirometric examinations.

Management of OA is identical to that of non-OA with the additional caveat that the patient must be removed from any further exposure to the causative agent. Thera-

peutically, combination of anti-inflammatory and bronchodilator drugs are advocated. The use of pharmacologic treatment is not a substitute for complete avoidance. There is increasing evidence to support a dose-response relationship of occupational allergens of plant, animal, microbial, or man-made origin. One can foresee the day when there will be strict guidelines related to threshold values of allergen below which sensitization does not occur.^{89,90}

PROGNOSIS

The principle determinants of patient outcome subsequent to removal from the offending agent include the total duration of exposure, asthma severity at diagnosis, and the pathogenic mechanisms operative in the induction of OA.⁹¹ In addition, coexisting factors such as cigarette smoking, chronic sinusitis, and gastroesophageal reflux may also play an important role as prognostic modifiers.⁹² Removal of the patient with OA from the offending immunogen or irritant should result in clinical improvement (Fig 2). Chan-Yeung⁹³ studied 75 patients with western red cedar asthma and found that half recovered completely. A later follow-up study of 232 patients by the same group revealed that 60% had not completely recovered during a 4-year observation period.⁹⁴ Most motivated patients achieve good control and are capable of resuming full employment in an alternative job description. In instances where the diagnosis of OA was delayed, or where the patient did not heed warnings about avoidance, chronic symptoms may remain indefinitely with concomitant pulmonary deterioration. Cote et al⁹⁵ reported on 48 patients with western red cedar asthma who had continuous exposure an average of 6.5 years after initial diagnosis. None of these patients had recovered and half demonstrated deterioration of lung function despite treatment.⁹⁵ Specific BHR to an inciting agent may persist after removal from further exposure in subjects who no longer show evidence of asthma symptoms, use antiasthma medications, or demonstrate nonspecific BHR.⁹⁶

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