

OCCUPATIONAL ASTHMA

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Occupational asthma is a unique clinical problem that has important medical, legal, and socioeconomic ramifications. Occupational asthma should be considered in the context of the evaluation and treatment of the difficult asthmatic because it can present many diagnostic and therapeutic challenges to the clinician. This article focuses on the practical issues that assist the physician in an accurate and timely diagnosis of occupational asthma so an appropriate management plan can be established and implemented.

Unfortunately, there is no simple universally accepted definition of occupational asthma. One straightforward definition is simply "the development of variable airways obstruction caused by inhalation of dusts, vapors, fumes or gases in the workplace."² This description suggests that documented airways obstruction does not necessarily need to be entirely reversible. Most authors stress that significant reversibility should be documented by an improvement of the forced expiratory volume in 1 second (FEV₁) of at least 12% to 15% or peak-flow improvement of 20% to 25%. In addition, it should be noted that this simple definition encompasses the possibility that occupational asthma may be superimposed on underlying nonoccupational asthma that has been worsened by workplace exposures.

Asthma is an increasingly common disorder with significant morbidity and mortality. Worldwide it is estimated that approximately 2% to 15% of all cases of asthma are occupational in origin.^{8, 14} Some 250 causative agents have been implicated in the induction of occupational asthma.¹² Though a detailed description of each of these agents is beyond the scope of this article, an attempt is made to review the most significant

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agents or groups of agents which may be capable of inducing occupational asthma.

The specific risk of developing occupational asthma is dependent on a variety of host factors and the nature and extent of occupational exposures. For example, workers in an isocyanate manufacturing plant have an approximate 5% risk of developing occupational asthma, and workers in high-exposure areas have the greatest risk.^{4, 5} At the other end of the spectrum, platinum refinery workers have been reported to develop occupational asthma at an alarming rate of up to 25%²⁷ with even more of these patients developing platinum-specific antibodies. Regardless of the occupation, because occupational asthma can be associated with significant morbidity, early recognition and detection of a symptomatic worker is critical. Timely removal of an affected individual from the workplace can result in complete resolution of asthma, whereas chronic exposure may lead to persistent asthma despite removal from the offending exposure.

RISK FACTORS

There are several risk factors for the development of occupational asthma that may also influence its presentation. These factors include:

- Atopy and aeroallergen exposure
- Cigarette smoking
- Coexisting respiratory infections
- Multiple medications including:
 - β blockers
 - Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - Angiotensin-converting enzyme (ACE) inhibitors
 - Susceptibility genes
 - Vocal-cord dysfunction
 - Chronic esophageal reflux

Atopy and coexisting aeroallergen exposures are clearly important factors in the presentation of occupational asthma. Individuals with underlying atopy are clearly more likely to respond to high-molecular-weight occupational aeroallergens.¹⁸ Individuals with coexisting aeroallergen exposures may have increased bronchial hyper-responsiveness as a result of these exposures. An individual may have underlying asthma on an allergic basis that may be worsened pathologically or symptomatically by occupational exposures. Despite the fact that cigarette smoking is banned in many workplaces, millions of workers continue to smoke on and off the job. Individuals who smoke cigarettes may have previously unrecognized chronic bronchitis that may be associated with bronchial hyper-responsiveness. When evaluating a patient with suspected occupational asthma, inquiries should be made into abuse of cannabis and other inhaled recreational drugs which may incite a significant respira-

tory inflammatory or irritant response. Workers with coexisting respiratory infections such as bronchitis or sinusitis may have symptoms that may mimic occupational asthma such as cough, shortness of breath, and audible wheezing. These infections may be associated with underlying bronchial hyper-responsiveness that further confounds the interpretation of pulmonary functions obtained in evaluation of an individual with suspected occupational asthma. The use of multiple medications should be considered a confounding variable in the evaluation of a patient with suspected occupational asthma. The use of β blockers may be associated with increased asthmatic symptoms. The use of NSAIDs in susceptible individuals can result in asthmatic responses. The well-recognized cough associated with the use of ACE inhibitors can further complicate the individual's evaluation.

The genetics of asthma are just beginning to be understood. No doubt, asthma is polygenic in origin. Considering occupational asthma only develops in a minority of potentially exposed patients, it is assumed that there are individual genetic predisposing factors that are involved with the induction of occupational asthma. It has been estimated that 40% to 50% of asthmatic subjects have a hereditary component.³ It has been proposed that specific HLA Class II immune responses are important genetic host factors in occupational asthma antigens.¹⁹ HLA markers have been reported in increased frequency in patients with isocyanate-induced asthma^{1,7} and in patients who have had acid anhydride-induced asthma.³² The frequency of HLA-DR1 and DR4 seem to be increased slightly in one group of reported latex-sensitized subjects.²⁶ The increased frequency in some patients of HLA Class II antigen expression suggests that there are important immunologic mechanisms involved with occupational asthma beyond the induction of antigen-specific immunoglobulin E (IgE). It is likely that multiple genes are responsible in those patients who have developed occupational asthma to a sensitizing or a nonsensitizing agent. Further work is required to fully understand these concepts.

Vocal-cord dysfunction is an increasingly common primary and secondary diagnosis in patients with any type of asthma.^{20, 22, 26} It is important to note that when patients present with upper respiratory symptoms such as choking or throat tightness, it does not rule out a diagnosis of occupational asthma and may be a secondary phenomenon associated with the anxiety of suspected or perceived dangerous exposures.

Gastroesophageal reflux is a disorder that is extremely common in the general population. It has been associated clearly with the induction or perpetuation of asthmatic signs or symptoms.³¹ Clearly, individuals with underlying gastroesophageal reflux may induce cough irrespective of the underlying asthma which can further complicate interpretation of suspected asthmatic symptoms.

CLINICAL PRESENTATION

When a physician considers the diagnosis of occupational asthma, there are many potential mechanisms of injury and disease that may be involved. Because of these multiple mechanisms, there is considerable confusion regarding the specific nomenclature of clinical presentations. Though the following diagnoses are considered distinct conditions by many experts, they also could be considered variants of occupational asthma because they fit the broad definition of variable airflow obstruction followed by occupational exposures.

Occupational Asthma Caused by Sensitizing Agents

As previously described, there are hundreds of potential high- and low-molecular-weight substances that can result in the appearance of occupational asthma caused by immunologic sensitization. The term *sensitization* implies that there has been a recognition of a substance by the immune system as foreign. This process does not occur immediately and requires a latency period between the time of initial exposure and the development of clinical sensitization. The latency period is variable but characteristically occurs over weeks to months. Following this latency period, during which immunologic sensitization takes place, subsequent exposures may result in both immediate and delayed reactions. Immunologic sensitization occurs with chronic low-dose exposure or over a shorter period of time with higher doses of exposure to an offending substance. This form of asthma sometimes is referred to as "classic occupational asthma." It is important to note that though sensitization classically occurs through high-molecular-weight substances such as large proteins, low-molecular-weight substances such as chemicals also can induce specific sensitization. In the setting of occupational asthma induced by low-molecular-weight chemicals, multiple mechanisms in addition to IgE-mediated sensitization may be important. A list of highly implicated high- and low-molecular-weight antigens and their associated industries is included in Table 1.

Though occupational bronchitis is considered a distinct clinical syndrome from occupational asthma, some cases of occupational bronchitis may be associated with reversible airways obstruction. The classic definition of chronic bronchitis may not be entirely relevant in the setting of occupationally induced bronchitis. Chronic bronchitis, by definition, is a condition that presents with cough for more than 3 months in 2 consecutive years. Chronic bronchitis typically occurs in the setting of chronic cigarette consumption. When chronic cough follows an occupational exposure to inhaled particulate matter of volatile substances in the workplace, the condition is referred to as occupational bronchitis. Though a latency period may be observed between initial exposure and cough, immunologic sensitization is not felt to occur during the latent period in this particular condition. Chronic bronchitis or occupational

Table 1. SELECTED AGENTS CAUSING OCCUPATIONAL ASTHMA

Agents	Industry
Low molecular weight	
Acid anhydrides	Surface coatings
Isocyanates	Pain, foam, plastics
Ethylenediamine	Beauty, plastics
Fluxes	Electronics
Antibiotics	Pharmaceutical
High molecular weight	
Latex	Health care
Animal danders/allergens	Laboratory workers
Fish	Seafood processing
Enzymes	Detergent
Insects	Grain handlers

bronchitis can be associated with reversible airways obstruction in approximately 25% of cases. When this occurs, individuals may have typical symptoms of wheezing and chest tightness with decrements in peak flow or FEV₁.

Reactive airways dysfunction syndrome (RADS) was first described in 1981.⁹ At that time a series of workers were described who had developed acute and chronic asthmatic symptoms following exposure to high levels of respiratory irritants. These workers presented with a condition that previously had been described as inflammatory bronchoconstriction. Individuals with inflammatory bronchoconstriction had been described decades earlier as developing rapid onset of airway obstruction following high-dose exposure to irritating chemicals.¹³ Previous pathologic studies have indicated that some of these patients had developed hemorrhagic pulmonary edema. Subsequently the diagnostic criteria for RADS has emerged which has improved understanding of this condition. A consensus criteria from the American College of Chest Physicians was outlined for the establishment of RADS.¹¹ The criteria include: (1) documented absence of preceding respiratory complaints, (2) onset of symptoms after a single exposure incident or accident, (3) exposure to very high concentrations of a gas, smoke, fume, or vapor with irritant properties, (4) onset of symptoms within 24 hours after exposure with persistence of symptoms for at least 3 months, (5) symptoms simulating asthma with cough, wheeze, and dyspnea, (6) presence of airflow obstruction on pulmonary function testing or presence of nonspecific bronchial hyper-responsiveness, and (7) all other pulmonary diseases excluded. Chemicals that have been implicated in the induction of RADS include toluene diisocyanate, chlorine, phosgene, sulfuric acid, phosphoric acid, hydrochloric acid, hydrogen sulfide, and anhydrous ammonia. The prognosis of RADS has been reported as variable. In some patients, complete resolution of symptoms and normalization of pulmonary function have occurred. Other patients have had significant long-term physiologic and symptomatic respiratory sequelae.

Direct pharmacologically induced bronchoconstriction can occur as a result of exposure to some substances. The classic case of pharmacologic bronchoconstriction occurs following inhalation of dusts associated with cotton, flax, hemp, or jute. This condition is referred to as byssinosis. The syndrome has been described in the medical literature for over 250 years. Patients who present with byssinosis classically present with symptoms of chest tightness, cough, wheezing, and shortness of breath following acute exposure to dust. The most pronounced symptoms occur at the beginning of the work week with more pronounced symptoms occurring the longer the worker is away from the workplace. Chronic exposure can result in brown lung disease. Although the precise mechanisms of byssinosis are poorly understood, it is believed this condition is caused by exposure to the natural histamine content of the dust and ability of the dust to directly release histamine from respiratory mast cells without sensitization. In addition to the example of byssinosis, pharmacologic bronchoconstriction also has been described following inhalation to organophosphate insecticides. Organophosphates can affect the lung by interfering with normal cholinergic control of airway caliber. In both of these conditions, inflammatory mechanisms are not considered the primary mode of action.

DIAGNOSIS

The medical history is the single most critical component necessary to establish a diagnosis of occupational asthma. The exact description of upper and lower respiratory complaints must be established before and subsequent to the occupational exposures. One then must define clearly the nature and time of the onset of symptoms experienced during the time the worker was exposed in the workplace. As previously outlined, the classic occupational asthma presentation involves a latency period of exposure to the offending compound without symptoms during which sensitization is taking place. Other critical elements in the medical history include a complete occupational history noting previous employment and potential exposures. A detailed description of the current workplace must be undertaken with descriptions of relevant air-quality data. The use of respiratory protective devices in the workplace should be recorded carefully. Review of the material safety data sheet (MSDS) may help to identify substances present at the workplace that may be potentially harmful to a worker. It is a legal requirement that workplaces that contain potentially hazardous materials must keep active files of MSDSs to which workers and their health care providers have direct access. In addition to occupational exposures established by the history and environmental history, comprehensive history must include nonoccupational exposures such as active or passive cigarette exposure. It is important to detail the potential exposure to indoor and outdoor pets that may induce an allergic or inflammatory response. Hobbies and avocations that would predispose the worker to exposure to potential

irritating or allergenic exposures must be detailed. Social habits such as the use of marijuana or other recreational drugs can be potentially important because the use of these drugs as previously outlined may induce or perpetuate an inflammatory response. Physical examination must be performed with detail and accuracy. Because of the intermittent nature of asthma, affected workers may exhibit normal physical findings. A normal physical examination does not rule out the presence of occupational asthma. In addition to a detailed examination of the upper and lower respiratory tract, physical examination also should direct attention to the skin and other mucosal surfaces which may have had previous or ongoing contact with potentially irritating or inflammatory chemicals or substances. The physical examination frequently may detect signs of pre-existing or coexisting illnesses that may present with symptoms or signs similar to occupational asthma.

Once a history and physical examination has been performed, every effort should be made to obtain and review previous medical records. These records often are invaluable for documenting objective findings at the time of previous symptoms which prompted the worker to receive medical attention. Many times workers forget that they may have been treated in an emergency room, for instance, with wheezing associated with respiratory tract infections or may have been treated on multiple occasions for previous infection. These are important findings when attempting to isolate specific causation of a condition, or demonstrating pre-existing asthma.

Diagnostic testing for occupational asthma usually includes objective measurement of pulmonary function such as the use of peak flow monitoring in and away from the workplace. Serial peak-flow monitoring may be helpful to determine the impact of an occupational exposure on potential airway obstruction. It should be noted that the main limitation of peak-flow monitoring is its requirement for a reproducible effort by the worker in the absence of testing supervision. Not all workers with occupational asthma exhibit significant day-to-day variations in peak flow correlating with exposure to the offending agents. It also has been noted that in the setting of a workers' compensation claim, peak-flow monitoring may not be a reliable indicator of airways obstruction.¹⁷ Spirometry offers the advantage of providing more information regarding the nature of patient's lung function including the ability to discriminate airflow obstruction patterns in the setting of normal peak flows. Spirometry also can identify restrictive patterns that typically are not identified with peak-flow monitoring. Spirometry has the potential for confirming the diagnosis of asthma based on significant improvement of FEV₁ following the use of inhaled bronchodilator by 12% to 15%. Formal pulmonary function studies including total lung volumes and single-breath carbon-monoxide diffusing capacity (DLCO) can be important in determining the full extent of a patient's pulmonary disorder. The presence of a diminished DLCO₂, for instance, would be more important in establishing a diagnosis of pre-existing chronic obstructive pulmonary disease caused by cigarette smoking when compared with

asthma which is classically associated with normal or increased DLCO₂. When clinical history, physical examination, and peak-flow monitoring or spirometry do not establish the presence of reversible airways obstruction, specific or nonspecific bronchial challenge frequently is necessary. Nonspecific bronchial challenge is undertaken with methacholine or histamine inhalation in controlled settings. Resolution of nonspecific hyper-responsiveness may occur within a few days following cessation of work exposure,²¹ but in some cases may persist for weeks or months. In most instances, it is not practical to perform a histamine or methacholine challenge in the workplace. Despite the limitations of methacholine or histamine challenge, a negative histamine or methacholine challenge essentially rules out asthma. Specific challenge to a suspected workplace agent can be undertaken in uncontrolled or controlled settings. Reproducing the patient's workplace environment in the pulmonary function laboratory can be difficult. Obtaining spirometric data immediately before and after working sometimes can be a useful alternative. Specific challenge in a controlled environment can be useful but is time consuming and sometimes difficult to interpret. For a specific challenge to be undertaken, one must frequently obtain prechallenge information on the degree of bronchial hyper-responsiveness with methacholine or histamine. Ideally, a specific challenge should be undertaken in a challenge chamber where there are no environmental variables that would interfere with the interpretation of the test. The patient should be monitored for immediate and delayed responses that can occur as long as 12 hours following the initial exposure. Because of the requirements of generating specific chemicals and close observation during and following the specific challenge, this monitoring can be time consuming and expensive. Despite the limitations of specific challenge, this method can be at times the only way of reliably establishing the diagnosis of occupational asthma and should be considered a gold standard.

Establishing the presence of a potential immunologic sensitivity is a critical component of establishing a diagnosis of occupational asthma. Unfortunately, well-validated immunologic testing is not available for many of the suspected occupational agents that may result in asthma. Exceptions to this include latex for which diagnostic testing is available by both in vitro and skin-testing methodology. Standardized tests have been developed for in vitro testing for latex, although a standardized skin-testing reagent is not yet commercially available.³⁴ Skin-test reagents to several other high-molecular-weight compounds associated with occupational asthma are available including animal danders and foods. An important limitation of even well-validated skin-test reagents stems from the fact that a positive test suggests exposure and sensitization and does not establish the cause and effect relationship of this previous sensitization to the presence of occupational asthma.

Low-molecular-weight compounds have been associated with the production of non-IgE antibodies and lymphocyte proliferation. Unfortunately, the test availability for IgG, IgM, or lymphocyte proliferation to

occupational allergens is extremely limited. In addition, the diagnostic validity of these tests have not been proven in large groups of patients.

PATHOPHYSIOLOGY

The pathophysiologic mechanisms that underlie occupational asthma are based on the same immunologic principles that apply to other hypersensitivity disorders. Immunologic sensitization regardless of whether the antigen is occupational or otherwise requires antigen processing and presentation by specialized antigen-presenting cells. These antigen-presenting cells then may present the antigen to T lymphocytes which further direct the immunologic response. For most occupational antigens, the activated T lymphocytes subsequently direct B lymphocytes to produce specific IgE antibodies. Other potential mechanisms include the production of IgG antibodies and activation of possible cytotoxic T lymphocytes. As previously stated, these mechanisms are under the control of immunologic response genes that seem to be responsible for a potential genetic predilection in many patients with occupational asthma.

Most studies in the occupational asthma literature have focused on antibody-dependent or antibody-mediated reactions. Antigen-specific IgE seems to be more common in occupational asthma caused by sensitization from high-molecular-weight proteins.²⁴ Some individuals with occupational asthma caused by low-molecular-weight substances such as platinum, diisocyanates, and plicatic acid also may have antigen-specific IgE.^{6, 10, 16, 30} It should be emphasized that the presence of antigen-specific IgE does not in and of itself establish a diagnosis of occupational asthma, as many exposed individuals without disease may have evidence of these antibodies. Specific IgG antibodies are present in some patients who have been sensitized to diisocyanates. The presence of isocyanate-specific IgE has been noted to be a highly specific but insensitive measure of occupational asthma induced by these agents.²⁹ Most investigators in the field of occupational asthma believe that there are multiple mechanisms involved in the pathophysiology of isocyanate asthma, including antibody-dependent mechanisms and direct toxicologic and pharmacologic effects of these low-molecular-weight substances. The acid anhydrides are a group of low-molecular-weight substances which, like isocyanates, are highly reactive and capable of inducing IgE and IgG antibodies. The diagnostic sensitivity of antigen-specific IgE to the acid anhydrides such as phthalic anhydride or trimellitic anhydride has been shown to be very high.²³

Clearly, cellular mechanisms and antibody-dependent mechanisms are important in some forms of occupational asthma. TH2-dependent cytokines such as interleukin-4 (IL-4) and IL-5 have been shown to be important in the pathogenesis of nonoccupational asthma. Non-IgE-dependent proinflammatory cytokines have been described in patients with isocyanate-induced occupational asthma.¹⁵

NATURAL HISTORY

The natural history of occupational asthma is sometimes unpredictable and frequently affected by pre-existing or coexisting disease states (see Table 1). For example, individuals with severe underlying asthma before their occupational exposures may respond differently to an offending agent than individuals without pre-existing disease. The presence of cigarette smoking is a common comorbid factor in interpreting the natural history of reversible airways obstruction in workers exposed to potential asthma-inciting agents. In the classic case of a worker without pre-existing or coexisting disease, timely removal of the worker from the offending exposure can result in complete resolution of the condition. It is important to recognize that some individuals may have complete resolution of symptoms but still maintain a significant level of underlying bronchial hyper-responsiveness to the offending agent or to nonspecific triggers such as methacholine. Additionally, some individuals may maintain immunologic sensitization for months to years following complete resolution of clinical disease. It is arguable as to whether immunologic sensitization in this setting is representative of a true disease state.

The medical literature supports the contention that individuals with documented occupational asthma following long-term or high-dose exposure may have chronic persistent disease. Large retrospective reviews have indicated that as many as 50% of individuals exposed to a potential asthma-inducing substance in the workplace may have chronic illness despite removal of the worker from the exposure. In patients who have recovered fully from occupational asthma, certain factors seem to be important. A significantly shorter duration of symptoms before establishing a diagnosis is associated with a more rapid resolution in symptoms. In addition, the degree of impairment in FEV₁ or in methacholine responsiveness also seems to be associated with the extent of resolution. Patients with lower FEV₁ and higher nonspecific airways hyper-responsiveness at the time of diagnosis tend to have greater persistence of asthma signs and symptoms. Other data have indicated that with careful control of ambient levels of offending agents the risk of chronic occupational asthma may be lessened.²⁸ An example of this phenomenon occurred in the setting of occupational asthma caused by latex. As previously discussed, latex is an increasingly recognized cause of occupational asthma, primarily in health care settings. It has been shown that individuals with occupational asthma caused by latex exposure can have complete resolution of their symptoms when transferred to a worksite in which nonpowdered latex gloves are in use. This resolution is most likely the result of decreased exposure to airborne allergens. Latex-induced occupational asthma is also an example of occupational asthma which is highly associated with underlying atopy. In these cases, in which the affected individuals have atopic genetic predispositions, one must consider the role of a nonwork environment in the induction or perpetuation of chronic or intermittent reversible airway obstruction. Despite the unpredictable nature of the natural history of occupational

asthma in many cases, it is essential that the treating physician focus on a timely removal of the individual from the offending worksite until a definite diagnosis is established.

TREATMENT

Once the diagnosis of occupational asthma has been established, the proper treatment involves the reduction of exposure to the offending agent and, if necessary, appropriate medications. Proper environmental control often necessitates complete removal from potential exposure. It is sometimes possible to modify the workplace by substituting an alternative agent for the allergenic one while continuing the worker's same job description. An example of this is replacing latex gloves with vinyl gloves in a workplace of a latex-allergic patient who requires routine glove use to perform his or her job. Substitutions are often not possible, however, especially in manufacturing industries where the occupational agent is an essential part of the production process. In these instances, workers with occupational asthma must be removed entirely from the workplace. Often, larger companies are able to retrain the worker to perform an alternate job that is free from exposure to the agent responsible for the occupational asthma. When this happens, the worker should retain his or her usual income during the retraining process and should not be paid less for the new job duties than he or she had been receiving previously. Other ways of accommodating workers with occupational asthma include changing ventilation characteristics in the workplace air supply or having the worker wear a respiratory mask to further reduce potential exposure. Rational decision making regarding avoidance of specific substances in the workplace often requires a professional environmental assessment of the workplace.

Medical treatment of occupational asthma is the same as the treatment applied to nonoccupational asthma. When chronic inflammation is suspected in the lower airways, anti-inflammatory therapy is indicated (e.g., oral or inhaled corticosteroids). Patients also should receive treatment with bronchodilators (usually an inhaled β -adrenergic agent such as albuterol), which only may be necessary on an as-needed basis. The use of leukotriene modifiers has not been studied systematically in this setting, although this addition to inhaled corticosteroids clearly would be reasonable in many cases.

SUMMARY

Occupational asthma continues to provide a challenge for primary care and consulting physicians. Because occupational asthma is the most common occupational pulmonary disease, practitioners must have a working knowledge of this complex condition. Because early recognition may improve long-term outcome, it is incumbent on the treating physi-

cian to identify potential cases and remove the worker from the potential offending source. The multiple confounding medical, socioeconomic, and legal variables in most cases requires that each patient be investigated rigorously, including review of past medical records, industrial hygiene data, and MSDs.

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