

Occupational exposures as triggers of asthma

Paul G. Vigo, MD, Mitchell H. Grayson, MD*

*Department of Medicine, Division of Allergy and Immunology,
Washington University School of Medicine, Campus Box 8122, 660 South Euclid Avenue,
St. Louis, MO 63110, USA*

The influence of environment on laborers has been noted since ancient times. Hippocrates (460–370 BC) observed that workers handling agricultural grains and products seemed to have more frequent respiratory complaints than workers in other trades. In the early 1700s, Ramazzini, the father of occupational medicine, wrote a discourse about the maladies of grain handlers [1]. Whether these people had pneumoconiosis or asthma is hard to determine. Nonetheless, Hippocrates and Ramazzini showed an increased awareness of factors in the environment that have an impact on the health of laborers. Factories and manufacturing plants abound with fumes, particles, dusts, and gases that can trigger respiratory symptoms upon exposure.

Respiratory complaints rank second to dermatologic manifestations as the most prevalent work-related disorders worldwide, and occupational asthma (OA) is the most common nonacute occupational lung disease of this group [2]. By the mid-1990s, approximately 250 agents had been identified as possible causes of OA [3]. With the introduction of new organic and inorganic chemicals, the list continues to grow. The clinician has the responsibility to identify patients suffering from OA and better manage their disease to minimize morbidity.

OA is characterized by variable airflow limitation and airway hyper-responsiveness directly attributable to a particular work environment. This airflow obstruction is brought about by inflammation of the respiratory tract and is frequently reversible. Although the presumed environmental agents may not be elucidated in all cases, the patient may be diagnosed with OA. Somewhat controversial is how to deal with evidence of pre-existing asthma in making the diagnosis of OA. The American College of Chest Physicians argues that asthma

* Corresponding author.

E-mail address: mgrayson@wustl.edu (M.H. Grayson).

antedating the occupational exposure precludes the diagnosis of OA; however, Wagner and Wegman [4] have proposed a new definition of OA that includes pre-existing asthma exacerbated by occupational triggers.

Because more cases of OA are being identified, the economic, medico-legal, and social repercussions are difficult to ignore. Once a patient is diagnosed with OA, the employer should minimize and eliminate identified agents to protect the diagnosed employee and survey the work environment to verify that there are no potential exposures remaining that might endanger other workers. The OA patient should undergo work rehabilitation and proper retraining for another job if continuing the current job is not possible. In Quebec, it is estimated that this surveying, verifying, and retraining costs somewhere around CAD \$75,000 (approximately USD \$60,000) [5]. This figure is roughly the equivalent of 2 years' salary, which is the usual amount of time for retraining and job hunting if the patient cannot stay in his or her current employment [5,6]. A survey of 134 OA workers 2 years after diagnosis showed that the unemployment rate can be as high as 8%. This financial burden does not include compensation for medical care, which is needed for an indefinite amount of time by as many as 75% of OA patients (see Prognosis section). Adding to the overall burden are the cost of lost productivity, "pain and suffering," diminished quality of life from continued symptoms, and social displacement if the patient needs to relocate for a different job. Thus, the true financial cost of OA cannot easily or reliably be determined but is likely quite high. In this article we discuss the prevalence, etiology (including presumed causative agents), diagnosis, and treatment of this high-burden disease.

Prevalence

The prevalence of occupational asthma is unknown because of several factors that hinder estimates. First, development of *de novo* asthma in adults is common; often in these cases, the role of the workplace is overlooked. Second, development of respiratory symptoms may result in patients leaving a work environment before a diagnosis of OA can be made. Third, no appropriate reporting system or registry exists in most countries to monitor the disease. Complicating our understanding about OA is the fact that much of the published literature is derived from anecdotal reports, small series, or retrospective data with no prospective long-term studies. Additionally, physicians may be hesitant to make the diagnosis of OA. Some of this hesitancy may be explained by living in a litigious society where the burden lies with the patient and physician to prove the respiratory condition is a direct consequence of employment.

Some data are available on OA prevalence. Reports place the prevalence of OA at 5% to 25% of exposed workers. The widely varying OA prevalence figures come from different industries, presumably indicating that prevalence is dependent upon the putative agents involved [7,8]. Workers that are regularly exposed to di-isocyanate compounds report a 10% prevalence rate [8], whereas one of the highest prevalence rates quoted involves the platinum refining

industry, where one out of four chronically exposed workers are reported to develop OA [9]. From 5% to 15% of rubber industry and health care/lab workers have evidence of latex sensitization [10,11]. Up to 50% of these workers have some form of respiratory symptoms, the severity of which correlates with amount and duration of exposure. Health care workers who complain of rhinoconjunctival symptoms after inhalation exposure to powdered latex particles have a higher prevalence of OA. One estimate put the cumulative incidence of OA from latex exposure at 4.5% [12].

Despite the wide discrepancy in reported prevalence rates, it is believed that approximately 2% to 10% of asthma cases worldwide may have occupational triggers [13]. Of these, only 2% to 5% of cases likely developed asthma strictly from workplace exposures [14]. Therefore, the risk of OA is fairly low when examining all individuals in a society, but the risk rises substantially when the patient works in an environment where occupational triggers are abundant. In one study, 26% of all new cases of asthma in adults (15–55 years of age) were felt to be caused by exposures received at work [15].

Pathophysiology

Although certain occupations or industries have long been associated with increased prevalence of asthma among workers, the mechanism by which putative occupational “asthma triggers” induce disease remains unclear. Most patients do not report a family history of atopy or asthma. Similar to non-occupational asthma, other factors besides a history of atopy seem to play a significant role in the development of the disease.

Four mechanisms are postulated to explain the development of OA. The first two are broadly described as “occupational asthma with latency” because of the lag time between purported sensitization and appearance of symptoms. Both are immunologic in nature but can be differentiated by the ability of the putative agent to elicit an IgE response with exposure. The third mechanism attributes the symptoms to an irritant effect, and the fourth uses the pharmaco-physiologic action of the agent without participation of the immune system. The last two mechanisms (irritant and pharmaco-physiologic) can be thought of as “occupational asthma without latency” because symptoms appear nearly instantly after exposure to the offending agent. Table 1 highlights different clinical characteristics and proposed mechanisms for the four forms of occupational asthma.

The two “occupational asthma with latency” mechanisms can be divided by the purported role of IgE in the reaction. In the IgE-mediated explanation, high-molecular-weight (HMW) (ie, >5 kD) and low-molecular-weight (LMW) molecules are able to induce an IgE response on their own or after haptenation with a human protein, forming a functional antigen. This mechanism is also seen with inhalant allergens leading to typical allergic rhinitis or allergic asthma. The appearance of symptoms is usually preceded by a period of latency that may last months to years after first exposure or sensitization to the agent. During this time,

Table 1

Proposed mechanisms and clinical characteristics of occupational asthma

	Asthma with latency		Asthma without latency	
	IgE involved	No IgE involved	RADS	Pharmaco-physiologic
Agents implicated	HMW agents	LMW agents	Noxious chemicals	Organic or inorganic compounds
Atopic history	Commonly present	May or may not be present	May or may not be present	May or may not be present
Skin testing	Positive	Negative	Negative	Negative
Onset of symptoms after sensitization	Months to years, insidiously	Months to years, insidiously	Acutely after accidental exposure or insidiously with chronic exposure	Acutely after exposures
Pattern of inflammatory response	Biphasic (early and late)	Late or biphasic	Late or irregular	Late or irregular

Abbreviations: HMW, high molecular weight; LMW, low molecular weight; RADS, reactive airways dysfunction syndrome.

respiratory symptoms, if present, may not be as prominent as nasal or ocular ones. After specific IgE against the sensitizing agent has been produced, reintroduction of the occupational allergen leads to cross-linking of IgE antibodies on the surface of mast cells and basophils. This leads to degranulation of these cells with release of preformed and newly synthesized inflammatory mediators including histamine, cysteinyl leukotrienes, prostaglandins, cytokines, and other chemotactic factors. These substances initiate a cascade of events that manifest as an immediate or biphasic (immediate and late) inflammatory response.

The second immunologic mechanism does not seem to involve the formation of IgE antibodies. This mechanism is often invoked when LMW agents are the purported cause of OA. These agents generally induce a lone late or atypical inflammatory reaction [16,17]. There are studies showing a different mechanism separate from IgE-mediated that might be operative when these agents cause disease. For example, it is believed that isocyanates [18] and plicatic acid (a water-soluble, nonvolatile compound) from Western Red Cedar [19] may be able to elicit IgE and IgG antibody responses. In the case of Western Red Cedar asthma, only 20% of subjects were shown to have IgE against plicatic acid despite having symptoms [19]. Bronchial biopsies from these patients revealed activated lymphocytes in the bronchial mucosal wall. When incubated with plicatic acid, peripheral blood lymphocytes from these patients proliferate, suggesting that plicatic acid-specific T cell clones have been generated in affected individuals [20,21]. Whether the formation of specific IgE leads to disease or represents only a sign of exposure remains unknown. Even less well defined than the role of IgE is the role of antigen-specific IgG [22]. It is anticipated that further studies focusing on the role of the cellular immune response [20] to LMW agents may yield clues to the pathogenesis of OA.

The third mechanism (without latency) proposes a neurogenic reflex that may result from insult to the bronchial epithelium. This insult may be in the form of gases, fumes, particles, or vapor. The damage that ensues leads to epithelial denudation, mucus hypersecretion, increased bronchial smooth muscle tone, and inflammatory cell recruitment with subsequent fibrosis. The ability of the agent to cause harm depends on its physical and chemical properties rather than its ability to stimulate an immune response [23]. This is the mechanism of reactive airways dysfunction syndrome (RADS), an entity that was first described in 1981 by Brooks and Lockey [24]. Some of the more common agents believed to cause RADS include chlorine gas, phosgene, ozone, acids (sulfuric, phosphoric, and hydrochloric), dioxides (sulfur and nitrogen), anhydrous ammonia, and toluene diisocyanate (which can also cause asthma with latency) [23,25].

The fourth mechanism (without latency) involves the pharmacologic action of the agent causing symptoms during or immediately after exposure. A classic example of this type of reaction is exposure of the respiratory tract to organophosphates. These insecticides can cause mucus hypersecretion and interfere with the normal cholinergic control of airway caliber, leading to bronchoconstriction. Byssinosis is the development of bronchoconstriction, coughing, wheezing, or shortness of breath after inhalation of cotton, hemp, or flax dust. The underlying mechanism of byssinosis is not known but may be related to non-IgE-mediated degranulation of mast cells with subsequent release of histamine; therefore, antihistamines have a role in treatment of this disease [26]. Chronic exposure to these types of agents is thought to cause inflammatory responses that may lead to permanent remodeling of the airway.

Although these mechanistic models are convenient and relatively simple to comprehend, the actual operative mechanisms are likely more complex and may involve a combination of each of these processes. Further research is needed to more fully comprehend the mechanisms by which OA develops. Until this occurs, it is unlikely that OA-specific therapeutics will be developed or will have a significant hope of making an impact in this disease.

Common agents and occupational exposures

There are more than 250 identified putative causes of OA, and, in general, these agents are organic macromolecules or inorganic chemicals found, used, or produced in the workplace [3]. These compounds can be divided into two groups based on their molecular weights. Some common HMW and LMW agents are described in Table 2.

Most HWM agents are plant or animal proteins and polysaccharides that are able to induce an antibody (IgE) response on their own without the need for haptenization. Natural rubber latex has become an important sensitizer in the rubber, health care, and laboratory industries [10,27]. Wheat and rye flour are important causative agents in many cases of so-called “baker’s asthma.” In

Table 2
Common sensitizers and exposures

Occupation/industry	HMW agents	LMW agents
Sawmill/woodworking/ carpentry	Wood dust (mahogany, oak, California redwood)	Plicatic acid (Western Red cedar)
Health care	Latex (powdered gloves)	Ethylene oxide (sterilizer) Glutaraldehyde (sterilizer)
Lab workers	Laboratory animals (dander, excreta, serum, feathers) Papain powder (tissue digestion)	Formalin (tissue fixing)
Pharmaceuticals	Psyllium Pancreatic enzymes	Ampicillin/penicillin Piperazine Tetracycline Salbutamol
Bird/pigeon fanciers poultry industry	Avian proteins (feathers, droppings)	Amprolium HCl (antiparasitic)
Beauticians	Henna extract (dye)	Monoethanolamine Hexamethylamine Ammonium thioglycolate Persulfate salts
Textile/dye industry	Cotton, wool, hemp Weevils	Paraphenylenediamine (fur dyers) Anthraquinone methyl blue (cloth dyers)
Paint/epoxy/chemicals		(Anhydrides) trimellitic, phthalic, hexamethylene
Polyurethane/plastics		Toluene diisocyanate
Platinum workers		Platinum salts (refinery)
Platers		Sodium bichromate Nickel sulphate
Solderers		Colophony (flux) Propylene glycol
Welders		Nickel
Cement workers		Potassium dichromate
Grains/baking/brewing	Wheat, buckwheat, rye flour Hops (brewery) Flour mites <i>Aspergillus</i> spp	
Nursery/greenhouse	Spider mite (<i>Tetranychus urticae</i>)	
Seafood processing	Crab/prawn proteins	
Printing/book binding	Acacia and arabic gum	
Detergent manufacturing	<i>Bacillus subtilis</i>	

Abbreviations: HMW, high molecular weight; LMW, low molecular weight.

addition to the flour, these workers are exposed to products of the mold genus *Aspergillus*, flour mites, insect debris, and other contaminants, all of which are potential HWM agents [28]. Proteins found in mammalian dander, saliva, serum, and excreta are associated with disease in veterinarians, laboratory workers, and animal handlers or fanciers. The reported prevalence rate of sensitization to rat or mouse urinary allergen is as high as 30%, with as many as a third of these

individuals having symptoms of OA [29,30]. Nearly all avian species produce allergens found in their feathers and droppings. Even insect and arthropod handlers, such as entomologists and sericulturists, are exposed to allergens found in the wings and other body parts of moths, flies, grain weevils, and worms. Farmers, because of their contact with livestock and crops, are susceptible to sensitization to these mammalian-, avian-, and insect-derived allergens [31–33].

Other HWM agents that can induce asthma symptoms in the workplace include plant- and animal-derived enzymes. Pancreatic enzymes extracted from pig [34] include trypsin, lipase, and amylase, all of which are used in the pharmaceutical industry. Often enzymes of plant origin are used in food preparation, breweries, and pharmaceutical/research laboratories. Other enzymes that have been associated with the IgE-mediated mechanism of OA include papain [35,36] (a proteolytic enzyme from the papaya tree) and bromelain [37,38] (a pineapple-derived) enzyme.

LMW agents that may cause asthma symptoms include organic or small inorganic chemicals that are readily inhaled into the respiratory tract and are encountered in a variety of settings including workplaces in pharmaceutical manufacturing, automobile assembly, paint/plastics/adhesives manufacturing, electronics and welding, and chemical production. Among the LMW agents, diisocyanates and anhydrides are the most common [8]. Toluene diisocyanate (TDI) is a highly reactive compound that can denature biomolecules. Inhalation of TDI at high concentrations is irritating to the respiratory and nasal mucosa. Lower concentration contact is also dangerous: These exposures have been shown to cause sensitization and subsequent respiratory symptoms [39]. Anhydrides are also commonly encountered; they are used in plastics, epoxy resin, and paint manufacturing. Occupational exposure to high concentrations of trimellitic anhydride (TMA) can lead to lacrimation, rhinorrhea, coughing, shortness of breath, and hemoptysis in previously unexposed workers. Furthermore, sensitization can develop because TMA-protein, conjugate-specific IgE antibodies have been documented in patients having asthmatic symptoms [40]. Other commonly encountered LWM agents include metals and metal products handled by platers, solderers, welders, and workers in refineries, electronic, and chemical plants.

Symptomatology, history, and physical examination

Obtaining a detailed medical and occupational history is critical in evaluating a patient presenting with respiratory symptoms suggestive of OA. The history should be used to recreate a timeline of symptom onset and circumstances in and out of the workplace that surrounded the onset of symptoms. Ocular, skin, and nasal symptoms may be more prominent and may precede lower respiratory complaints, especially in OA with an extended latency period [12,41,42]. It is important to determine any aggravation or improvement of symptoms that is temporally related to the work schedule. OA complaints tend to worsen during

(or for several hours after) work [17]. Because symptoms occur after work hours, many employees (and providers) do not attribute the symptoms to work. Examples of this include patients with byssinosis frequently waking at night with coughing fits or patients who are sensitized to plicatic acid having significant nocturnal asthmatic attacks. Improvement of symptoms on weekends, vacations, or days off strengthens the hypothesis that the symptoms are due to a workplace exposure [14]. However, in some cases this pattern may not be evident, especially if there has been significant chronic inflammation between exposure episodes leading to the development of constant symptoms. The appearance of constitutional symptoms should also be noted because their presence widens the differential to include infections, tumors, hypersensitivity pneumonitis, or other inflammatory pneumonitides.

Personal and family history of atopy must be determined. Studies have shown that patients with atopy have a higher sensitization rate than those who do not have an atopic background [43]. This is most important when HMW antigens or other organic compounds are suspected as the causative agents. Atopic detergent workers or atopic workers who have been exposed to latex or laboratory animals show higher incidences of occupational asthma when compared with nonatopic workers in the same field [10,12,30,41]. Patients with aeroallergen allergies may have baseline bronchial hyper-responsiveness that may be aggravated further by additional or repeated exposure to agents encountered in the workplace.

In addition to pertinent medical questions, inquiries should be made about current and previous work situations, possible exposures, accidental spills, and adherence to Occupational Safety and Health Administration regulations. Questions as to whether colleagues are having similar symptoms and whether they work in the same area as the patient should be asked. The typical occupational health history contains questions such as What kind of work do you do? What does that involve? Are there any health hazards that you are aware of or concerned about?

It is advisable for the clinician to obtain materials safety data sheets from the employer to be able to learn of the properties and idiosyncrasies of chemicals and agents to which the worker was exposed. The duration and intensity of exposure should be determined. This allows for a better attempt at elucidating the extent of disease and possibly even the mechanism behind the symptoms. For example, a massive but short exposure to a particular agent instantly provoking ocular, nasal, and respiratory symptoms suggests RADS, not OA with latency, as the operative mechanism behind the symptoms [23].

During the evaluation, use of illicit drugs and cigarette smoking should be determined because these agents have irritant effects on the respiratory mucosa. Chronic smokers may have chronic obstructive pulmonary disease (COPD) that may be misdiagnosed as OA. Some evidence exists suggesting that cigarette smokers have a four to six times higher risk of OA upon exposure to platinum salts, laboratory animals, or acid anhydrides [44–46].

The physical examination should be thorough and complete. In addition to pulmonary findings, special attention should be directed to skin, ocular, oropharyngeal,

ryngeal, and nasal examinations because these may hold clues to the cause and mechanism involved. It is not surprising that in some cases the physical examination is normal, especially when the office visit occurs during the worker's vacation or days off when no recent exposure to the sensitizers has occurred.

Diagnosis

Although the history and physical examination may suggest OA, objective testing is needed to confirm the diagnosis. It is important to recognize that there is no gold standard test for OA; diagnosis is based on interpretation of subjective and objective data in the context of the clinical picture. A brief overview of the diagnostic approach and treatment of occupational asthma is given in [Box 1](#).

After taking a thorough history, it is important to confirm the presence of an atopic state, preferably by performing skin tests to common aeroallergens. Significant positive skin tests may suggest an allergic component to the symptoms. The patient may have subclinical asthma that has been unmasked by sensitizers or nonspecific irritants in the workplace. Skin testing for HWM agents encountered in the workplace may be of value in establishing a causal relationship between exposure and symptoms. To skin test to HWM agents, clinicians may have to resort to titration skin prick testing on non-exposed, nonatopic individuals to determine the minimum irritating concentration for a particular agent. One note of caution involves the unknown positive predictive value of a skin test to HWM agents: A positive skin test may not indicate IgE sensitization to the agent and may represent an irritant or nonspecific response.

Although skin testing may seem manageable for HMW agents, it is impractical or even impossible for most LMW agents. This is because for these agents to form functional antigenic determinants, they must become haptenedated with a

Box 1. Diagnosis and management of occupational asthma

1. Clearly document and understand progression of symptoms.
2. Obtain a good medical and occupational history.
3. Establish presence of atopy.
4. Document level of bronchial hyper-responsiveness.
5. Exclude all other possible causes of lung disease.
6. Minimize further exposure for patient and coworkers in the offending work environment (may involve change of duties or job).
7. Control bronchial hyper-responsiveness and symptoms.
8. Monitor pulmonary status over time.

serum protein. It is possible that the act of haptization changes the tertiary structure of the antigen-hapten complex that leads to the formation of conformational epitopes, which elicit production of specific IgE. Testing with the pure LMW agent alone, without haptization, may prove useless because may be unable to elicit a wheal and flare reaction, which indicates presence of specific IgE.

Serum-specific IgE antibodies to HWM and some LWM agents are available by radioallergosorbent testing or enzyme-linked immunoassay and may be used to confirm atopy as well. However, the presence of such antibodies does not necessarily indicate that IgE sensitivity causes the patient's symptoms. As in allergic rhinitis and asymptomatic bronchial hyper-responsiveness, positive test results can occur in asymptomatic patients with subclinical sensitization.

The next step in the diagnosis of OA is to document airway hyper-reactivity by pulmonary function tests (PFTs). Assessing forced expiratory volume in 1 second (FEV₁) and the response to a bronchodilator before, during, and after work is often useful in establishing the diagnosis. However, the logistics of this—a technician and equipment to administer pulmonary function testing at home and at work—often makes this a difficult task to undertake. A more viable option is to have the patient record peak expiratory flow using a handheld peak flow meter before, during, and after work, together with measuring response to bronchodilator treatment [44]. Improper technique by the patient, falsification of results, or the presence of nonspecific bronchial irritants in the workplace and at home may limit the usefulness of the recorded data. If bronchial hyper-responsiveness cannot be determined by any of these methods, a methacholine challenge must be performed. A negative methacholine challenge rules out OA because the patient must have some evidence of bronchial hyper-responsiveness for the diagnosis to be made. Parameters for a positive bronchodilator response, PEFR variability, and methacholine provocation are the same for diagnosing OA as those used in diagnosing non-occupational asthma.

Specific challenge testing to simulate the work environment is done at a few centers. Although this may be considered the gold standard by some clinicians, it is impractical and potentially fraught with false-positive or false-negative results. This is because the correct concentration, combination, and duration of exposure may not be duplicated or otherwise match that which would be encountered in the workplace. Furthermore, the choice of agent and its physical form (dust, vapor, gas, fumes, etc.) may affect the outcome of testing [47]. Finally, this kind of testing may be harmful to the patient, especially if it is done in a facility that does not regularly perform these tests and therefore has had little experience with these issues.

Newer diagnostic techniques are being investigated to evaluate their usefulness in diagnosing OA. Some of these tests include measurement of exhaled nitric oxide, sputum eosinophil counts, and exhaled breath pH. Rather than “ruling-in” OA, there are diagnostic tests that may be useful to “rule out” other causes for respiratory symptoms. A chest x-ray is a good screening test to look for signs of COPD, pneumonia, foreign bodies, and pneumonitides. A limited sinus CT is often useful to exclude chronic sinus disease if the patient has a

significant history and symptoms. Esophogastric pH monitoring or a therapeutic trial of an H₂ receptor blocker or proton pump inhibitor may be necessary to rule out any contribution of gastro-esophageal reflux disease to the symptoms. Tests that have not proven useful in the workup of OA and should be avoided include lymphocyte proliferation assays and quantification of total IgG or IgM [48].

Differential diagnosis

During the sensitization phase, the most prominent presenting symptoms may be cough and nasal catarrh. Because wheezing may not manifest until later in the course of disease, many patients are misdiagnosed early as having recurrent respiratory infections. Shortness of breath is not an early symptom of OA but may be present in RADS, especially if the agent is extremely noxious or the exposure significant. Symptoms of RADS usually occur immediately or within 24 hours and may persist for months without further exposure. This is in contrast to OA where symptoms occur hours, if not days, after exposure (this follows several weeks after the initial sensitizing exposure) and cease with avoidance of the offending agent.

Mimics of OA include non-occupational asthma and its masqueraders. With the current definition of OA, the patient cannot have a pre-existing or prior history of asthma. It is therefore critical to determine if the patient has asthma that was unmasked or aggravated by factors in the workplace rather than caused by those agents [43]. In addition to non-occupational asthma, the major diagnosis to consider in the differential is COPD. This is a common disorder in workers with a significant smoking history and a symptom complex that includes shortness of breath, wheezing, chest tightness, and cough. Vocal cord dysfunction (VCD), another asthma masquerader, should be considered as a cause of symptoms similar to that seen in OA. VCD is more common in young adult women, competitive athletes, or patients with significant psychologic factors affecting their life [49]. Although VCD is often mistaken for asthma, it may present as acute shortness of breath where the perceived blockage is in the “throat” area, and symptoms often develop when the patient is engaged in some form of physical activity or exertion. The physiologic cause of VCD is paradoxical adduction of the vocal cords during inspiration leading to a localized obstruction of airflow into the lungs. A clue to the diagnosis is a flattened or attenuated inspiratory loop in the flow-volume curve during pulmonary function testing.

Occupational lung diseases, such as farmer’s lung, coal miner’s pneumoconiosis, silo filler’s disease, or chemical worker’s lung, can be mimics of OA. Patients with these conditions also present with work-related coughing, wheezing, chest tightness, and shortness of breath. These are not IgE-mediated diseases and do not cause obstructive disease (as assessed by PFT monitoring). Unfortunately, it is only retrospectively, or when index of suspicion is high, that these patients are worked up appropriately for OA.

Treatment

The management of occupational asthma is two pronged. The main principle is avoidance of further exposure and minimization of morbidity. To achieve this, exposure to the offending agent should be eliminated, and future exposures should be prevented. The employer should find a substitute for the offending agent or change the work process (engineering change). Alternatively, the employee could be moved within the company to a location where there is no risk of exposure. If these strategies cannot be implemented, use of personal respiratory protective equipment should be considered. Adherence to this avoidance measure is critical, and this approach must be emphasized to the patient. If the use of protective gear is impractical or impossible, then a change in occupation or trade may be the only acceptable alternative. Because factors outside of the workplace may aggravate symptoms due to existing inflammation in the respiratory tract, cigarette smoke, strong odors, dusts, humidity, cold air, or heavy aeroallergen exposure should be avoided as much as possible.

The second direction of treatment is to control the underlying respiratory inflammation. This can be achieved using the same pharmacologic agents as are used to treat non-occupational asthma. Even though no formal guidelines for assessing and treating OA exist, the clinician can be guided by the stepwise approach of the National Asthma Education and Prevention Program/Global Initiative for Asthma guidelines (available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm). It may be necessary to use a burst of oral corticosteroids to abate an acute or a severe episode. Maintenance inhaled corticosteroids may be used as controller therapy to diminish persistent airway hyper-responsiveness. Inhaled short-acting beta-agonists may be used as rescue medication. Specific immunotherapy injections may not be useful unless sensitivity to animal dander is the known cause of OA. However, pharmacotherapy alone treats symptoms but does nothing to resolve the underlying cause of disease; this is why primary therapy must be avoidance of the offending agent. Avoidance lessens the severity of the patient's disease and allows for more effective pharmacologic treatment at lower doses with fewer potential side effects.

Prognosis

The prognosis of patients with OA depends on several factors. Duration and level of exposure [29,30,50], baseline lung function, degree of initial decline in FEV₁, and intrinsic factors relating to the sensitizing or irritating agents [51] seem to dictate the level of improvement the patient derives after prompt removal from the offending environment. In the case of western red cedar OA, about 50% of workers had resolution of their symptoms when removed from the workplace [52]. Other studies [40,53,54], however, have not shown such positive results—especially when avoidance is not stringently applied. In one series, most red cedar OA patients who continued to work in sawmills for more than 6.5 years conti-

nued to have symptoms, with a majority of patients deteriorating and fewer than 10% showing any improvement [55,56]. Prognostic factors are not well defined; however, patients whose bronchial hyper-responsiveness persisted continued to have symptoms for years even after switching employment [54,57]. Therefore, early removal from exposure is recommended to try and minimize morbidity. Identification of an index patient with OA should prompt an examination of the workplace for possible exposures, other workers that might be affected, and ways to prevent all workers, including asymptomatic ones, from additional exposures.

Summary

With diligent employers, inquisitive physicians, and compliant patients, the prevalence of OA and its impact on our society may decline in the near future. To achieve this requires that care providers routinely inquire about work and workplace exposures of all of their patients. Otherwise too many OA patients will go undiagnosed. Additional research on the mechanisms of OA and new treatments are needed so that we will be able to offer improved prognosis for those who do develop OA in the future.

Acknowledgments

We thank Deborah L. Grayson, RN, MSN, MPH, COHN-S, for helpful advice and critical review of this manuscript.

References

- [1] Pepys J, Bernstein IL. Historical aspects of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo J-L, et al, editors. *Asthma in the workplace*. 2nd edition. New York: Marcel Dekker; 1999. p. 299–322.
- [2] Centers for Disease Control and Prevention. National occupational research agenda. Washington, DC: National Institute for Occupational Safety and Health, US Department of Health and Human Services; 1996. Pub. No. 96-115.
- [3] Chan-Yeung M, Malo JL. Occupational asthma. *N Engl J Med* 1995;333:107–12.
- [4] Wagner GR, Wegman DH. Occupational asthma: prevention by definition. *Am J Ind Med* 1998; 33:427–9.
- [5] Dewitte JD, Chan-Yeung M, Malo JL. Medicolegal and compensation aspects of occupational asthma. *Eur Respir J* 1994;7:969–80.
- [6] Malo JL, Boulet LP, Dewitte JD, et al. Quality of life of subjects with occupational asthma. *J Allergy Clin Immunol* 1993;91:1121–7.
- [7] Beckett WS. The epidemiology of occupational asthma. *Eur Respir J* 1994;7:161–4.
- [8] Bernstein DI. Allergic reactions to workplace allergens. *JAMA* 1997;278:1907–13.
- [9] Cromwell O, Pepys J, Parish WE, et al. Specific IgE antibodies to platinum salts in sensitized workers. *Clin Allergy* 1979;9:109–17.
- [10] Fish JE. Occupational asthma and rhinoconjunctivitis induced by natural rubber latex exposure. *J Allergy Clin Immunol* 2002;110(Suppl):S75–81.

- [11] Liss GM, Sussman GL. Latex sensitization: occupational versus general population prevalence rates. *Am J Ind Med* 1999;35:196–200.
- [12] Archambault S, Malo JL, Infante-Rivard C, Ghezzo H, Gauthrin D. Incidence of sensitization, symptoms, and probable occupational rhinoconjunctivitis and asthma in apprentices starting exposure to latex. *J Allergy Clin Immunol* 2001;107:921–3.
- [13] Blanc PD, Eisner MD, Israel L, Yelin EH. The association between occupation and asthma in general medical practice. *Chest* 1999;115:1259–64.
- [14] Tarlo SM, Leung K, Broder I, Silverman F, Holness DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. *Chest* 2000;118:1309–14.
- [15] Milton D. Risk and incidence of asthma attributable to occupational exposure among HMO members. *Am J Ind Med* 1998;33:1–10.
- [16] Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Med* 1982;72:411–5.
- [17] Perrin B, Cartier A, Ghezzo H, et al. Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol* 1991;87:630–9.
- [18] Cartier A, Grammer L, Malo JL, et al. Specific serum antibodies against isocyanates: association with occupational asthma. *J Allergy Clin Immunol* 1989;84:507–14.
- [19] Chan-Yeung M. Mechanism of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Ind Med* 1994;25:13–8.
- [20] Frew AJ, Chan H, Lam S, Chan-Yeung M. Bronchial inflammation in occupational asthma due to western red cedar. *Am J Respir Crit Care Med* 1995;151:340–4.
- [21] Frew A, Chan H, Dryden P, Salari H, Lam S, Chan-Yeung M. Immunologic studies of the mechanisms of occupational asthma caused by western red cedar. *J Allergy Clin Immunol* 1993;92:466–78.
- [22] Grammer L, Shaughnessy M, Kenamore B. Utility of antibody in identifying individuals who have or will develop anhydride-induced respiratory disease. *Chest* 1998;114:1199–202.
- [23] Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376–84.
- [24] Brooks SM, Lockey J. Reactive airways disease syndrome (RADS): a newly defined occupational disease [abstract]. *Am Rev Respir Dis* 1981;123(Suppl):A133.
- [25] Alberts WM, Brooks SM. Reactive airways dysfunction syndrome. *Curr Opin Pulm Med* 1996;2:104–10.
- [26] Montanaro A. Occupational asthma. *Immunol Allergy Clin North Am* 2001;21:489–501.
- [27] Hunt LW, Fransway AF, Reed CE, et al. An epidemic of occupational allergy to latex involving health care workers. *J Occup Environ Med* 1995;37:1204–9.
- [28] Quirce S, Polo F, Figueredo E, Gonzalez R, Sastre J. Occupational asthma caused by soybean flour in bakers: differences with soybean-induced epidemic asthma. *Clin Exp Allergy* 2000;30:839–46.
- [29] Hollander A, Heederik D, Doekes G. Respiratory allergy to rats: exposure-response relationships in laboratory animal workers. *Am J Respir Crit Care Med* 1997;155:562–7.
- [30] Venables KM. Low molecular weight chemicals, hypersensitivity, and direct toxicity: the acid anhydrides. *Br J Ind Med* 1989;46:222–32.
- [31] Lutsky I, Teichtahl H, Bar-Sela S. Occupational asthma due to poultry mites. *J Allergy Clin Immunol* 1984;73:56–60.
- [32] Kronqvist M, Johansson E, Pershagen G, Johansson SG, van Hage-Hamsten M. Increasing prevalence of asthma over 12 years among dairy farmers on Gotland, Sweden: storage mites remain dominant allergens. *Clin Exp Allergy* 1999;29:35–41.
- [33] Kronqvist M, Johansson E, Pershagen G, Johansson SG, van Hage-Hamsten M. Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. *Allergy* 1999;54:1142–9.
- [34] Aiken TC, Ward R, Peel ET, Hendrick DJ. Occupational asthma due to porcine pancreatic amylase. *Occup Environ Med* 1997;54:762–4.

- [35] Baur X, Konig G, Bencze K, Fruhmann G. Clinical symptoms and results of skin test, RAST and bronchial provocation test in thirty-three papain workers: evidence for strong immunogenic potency and clinically relevant 'proteolytic effects of airborne papain'. *Clin Allergy* 1982;12: 9–17.
- [36] Milne J, Brand S. Occupational asthma after inhalation of dust of the proteolytic enzyme, papain. *Br J Ind Med* 1975;32:302–7.
- [37] Galleguillos F, Rodriguez JC. Asthma caused by bromelin inhalation. *Clin Allergy* 1978;8:21–4.
- [38] Gailhofer G, Wilders-Truschnig M, Smolle J, Ludvan M. Asthma caused by bromelain: an occupational allergy. *Clin Allergy* 1988;18:445–50.
- [39] Raulf-Heimsoth M, Baur X. Pathomechanisms and pathophysiology of isocyanate-induced diseases: summary of present knowledge. *Am J Ind Med* 1998;34:137–43.
- [40] Grammar L, Shaughnessy M, Henderson J, et al. A clinical and immunologic study of workers with trimellitic-anhydride-induced immunologic lung disease after transfer to low exposure jobs. *Am Rev Respir Dis* 1993;148:547.
- [41] Gautrin D, Ghezzi H, Infante-Rivard C, Malo JL. Incidence and determinants of IgE-mediated sensitization in apprentices: a prospective study. *Am J Respir Crit Care Med* 2000;162:1222–8.
- [42] Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;10:1513–5.
- [43] Tilles SA, Jerath-Tatum A. Differential diagnosis of occupational asthma. *Immunol Allergy Clin North Am* 2003;23:167–76.
- [44] Moscato G, Dellabianca A, Maestrelli P, et al. Features and severity of occupational asthma upon diagnosis: an Italian multicentric case review. *Allergy* 2002;57:236–42.
- [45] Venables KM, Upton JL, Hawkins ER, Tee RD, Longbottom JL, Newman Taylor AJ. Smoking, atopy, and laboratory animal allergy. *Br J Ind Med* 1988;45:667–71.
- [46] Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Taylor AJ. Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *Br Med J (Clin Res Ed)* 1985;290:201–4.
- [47] Zacharisen MC. Occupational asthma. *Med Clin North Am* 2002;86:951–71.
- [48] Franz T, McMurray KD, Brooks S, Bernstein IL. Clinical, immunologic, and physiologic observations in factory workers exposed to *B. subtilis* enzyme dust. *J Allergy* 1971;47:170–80.
- [49] Newman KB, Mason III UG, Schmalung KB. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 1995;152:1382–6.
- [50] Baur X, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin Exp Allergy* 1998;28:537–44.
- [51] Montanaro A. Prognosis of occupational asthma. *Ann Allergy Asthma Immunol* 1999;83: 593–6.
- [52] Chan-Yeung M, Lam S, Koener S. Evaluation of impairment/disability in patients with occupational asthma. *Am Rev Respir Dis* 1987;135:9501.
- [53] Banks DE, Rando RJ, Barkman Jr HW. Persistence of toluene diisocyanate-induced asthma despite negligible workplace exposures. *Chest* 1990;97:121–5.
- [54] Hudson P, Cartier A, Pineau L, et al. Follow-up of occupational asthma caused by crab and various agents. *J Allergy Clin Immunol* 1985;76:682–8.
- [55] Cote J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. *Am Rev Respir Dis* 1990;141:373–6.
- [56] Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (*Thuja plicata*). *J Allergy Clin Immunol* 1987;79:792–6.
- [57] Malo JL, Cartier A, Cote J, Milot J, Leblanc C, Paquette L. Influence of inhaled steroids on recovery from occupational asthma after cessation of exposure: an 18-month double-blind crossover study. *Am J Respir Crit Care Med* 1996;153:953–60.