



Occupational asthma

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Occupational asthma is a major cause of pulmonary disease and the most common cause of nonacute occupational lung disease in the industrialized world. The relationship of the workplace to respiratory symptoms dates back to eighteenth-century work by Bernardo Ramazzini. It has been estimated that 2% to 10% of adult patients who present with asthma have triggers at the workplace [1,2]. Only 2% to 5% of cases likely develop strictly from workplace exposures, whereas 5% to 10% of adult asthma is exacerbated by factors at the workplace. Recent reports suggest that occupational asthma may be more common than previously thought.

The workplace is an area where the worker may be exposed to a variety of materials, gases, fumes, and particles that can induce pulmonary symptoms in a sensitizing or nonsensitizing manner. In an increasingly industrialized society where there is myriad of new polymers, plastics, and chemical exposures, it can be confusing to the public and to health care providers to determine which compounds induce annoyance reactions; irritant reactions with negligible to substantial inflammation; overt toxic reactions; or immediate or delayed hypersensitivity (allergic) reactions.

This article expedites and accomplishes the exercise in differential diagnosis of a patient presenting with lower respiratory symptoms or asthma in the context of the workplace. This requires knowledge of the potential causes and mechanisms of induction. Management of such pulmonary disease is equally challenging, because there are not only medical, but also legal and financial implications.

Definition

Occupational asthma is a disease characterized by variable or partial airways obstruction, usually reversible either spontaneously or with treatment,

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or bronchial hyperresponsiveness resulting from the inhalation of airborne agents present at the work place [3]. These agents may include vapors, dusts, gases, or fumes.

Occupational asthma can be divided into immunologic (IgE mediated) and nonimmunologic mediated disease. The importance of this distinction is realized later in the methods of evaluation for the causal agent. Less commonly, high-level exposure (single or multiple) to irritant agents can provoke symptoms of asthma without a latent period known as *reactive airways dysfunction syndrome* (RADS) [4]. This syndrome has no known defined immune etiology.

Despite the mechanisms or the inciting agent, the final common pathway is respiratory symptoms indistinguishable from nonoccupational asthma. It is the role of the clinician actively to engage in a series of steps to determine if a link exists between the work environment and exacerbation or initiation of asthma.

Epidemiology

The incidence of occupational asthma is imprecise, can vary widely depending on many factors including the specific agent involved and the methodology applied, and is likely underestimated both because of a failure to diagnose and a reluctance of the worker to complain about symptoms related to his or her job for fear of losing the job in a struggling economy [23]. The incidence of occupational asthma is variable between countries primarily because of the manner of how that country applies the definition. The source of information (worker's compensation or medical offices or clinics) can influence the reported frequency of occupational asthma. The tools used to document cases may vary and use of the gold standard test, specific inhalation challenge study, are not routinely used. There is a bias to underestimate the frequency of occupational asthma based on affected workers who leave the workplace coined the *healthy worker effect*. Using worker's compensation or legal cases as a measure of frequency is misleading, because some workers prefer not to pursue such avenues.

The frequency of occupational asthma during the 1990s in Quebec, Canada, was fairly stable for agents including flour, wood-dust, metals, and laboratory animals. The frequency decreased for pharmacologic agents and isocyanates but increased for latex [5]. A population-based, cross-sectional study of over 18,000 adults in urban Canadian communities revealed 383 who had asthma, of which 166 developed during adulthood. Occupational asthma was characterized as probable in 16% and possible in 20% of these groups. Most cases were suspected high-molecular-weight (HMW) agents, such as latex, grain, or biologic enzymes in occupations of nursing; baking; chemical, rubber, and plastics manufacturing; and hairdressers [6]. Enzymes used in detergent factories were first identified as causing occupational

asthma in the 1960s. Recently, cases of occupational asthma related to new proteases have resurfaced in detergent factories [7]. In Finland, analysis of health claim applications for asthma among employed adults over a 12-year period revealed that nearly 30% of men and 17% of women developed asthma that was linked to their occupation [8]. This significant increase from previous estimates is believed to be related to nonspecific irritants exacerbating worker's asthma rather than known specific sensitizers. It is estimated that 10% of laboratory animal handlers develop asthma, whereas nearly 100% of platinum refinery workers can become sensitized [9,27].

Individual susceptibility as determined by host responses and the inherent variability of asthma make it difficult to study occupational asthma epidemiologically. Furthermore, the degree of risk associated with occupational exposures is difficult to determine because of multiple exposures and the lack of sensitivity and specificity of the various diagnostic tests currently available. Nevertheless, a high index of suspicion is required when evaluating a patient with new-onset lower respiratory symptoms.

Pathogenesis and mechanisms

The clinical, functional, and pathologic changes in occupational asthma are similar to those found in nonoccupational asthma. These include the findings of (1) acute airway constriction related to airway smooth muscle constriction and mucosal edema; (2) airway wall thickening related to the influx and accumulation of inflammatory cells, mucus production, and sub-epithelial fibrosis; and (3) nonspecific bronchial airway hyperresponsiveness.

Immunologic occupational asthma

Occupational asthma that follows a latent period where sensitization occurs followed by symptoms on subsequent exposure is termed *immunologic asthma*. If the immunologic mechanism is a type I hypersensitivity reaction involving Th2 cytokines, then specific IgE antibodies directed against the antigen are responsible and invariably can be measured. Agents that induce the production of IgE are typically HMW proteins that act as complete antigens or low-molecular-weight (LMW) molecules or chemicals that combine with respiratory proteins that then act as haptens. The specific IgE antibodies that are directed against the haptenated chemical complex or protein bind to the surface of mast cells, basophils, and possibly alveolar macrophages and eosinophils. When the antigen or agent is subsequently inhaled and cross-links cell-bound IgE, a cascade of chemical mediators is released resulting in an influx of inflammatory cells and the additional release of inflammatory mediators. The end result is microvascular leakage, epithelial damage, reflex bronchoconstriction, neuropeptide and metalloproteinase involvement, and chronic airways inflammation.

The physicochemical properties of the agent that influence the immunogenic properties are molecular weight, chemical composition, complexity, conformation, foreignness, and reactivity with proteins. The deposition and clearance of the agents are additional factors. Table 1 lists a variety of triggers of occupational asthma.

Irritant-induced occupational asthma

Other agents act as respiratory irritants, inducing symptoms without a latent period. The physical properties that influence irritants are solubility; physical state (particles, fumes, gases, and vapors); and size or density and hygroscopicity (ie, the ability to evaporate). In these cases, the underlying mechanism is not completely known; however, the inflammation that is produced is believed to be a direct result of widespread denudation of the airway epithelium with loss of epithelial-derived relaxing factors, exposure of airway nerve endings, and nonspecific activation of airway cells leading to the release of inflammatory mediators and cytokines [6]. When these respiratory irritants are inhaled in high doses, the acute respiratory condition is termed *RADS* [24].

Multiple mechanisms

Some agents can induce occupational asthma by more than one mechanism. An example of this includes the LMW chemicals isocyanates, which at high airborne levels act as an irritant by stimulating nerve cells to release neuropeptides, such as substance P, and which at low levels can produce sensitization through haptentation with airway proteins, inducing IgE-mediated asthma. Additionally, isocyanates can induce occupational hypersensitivity pneumonitis that is primarily mediated by alveolar macrophages and CD8⁺ T lymphocytes resulting in dyspnea and hypoxemia with rales and a restrictive pattern on pulmonary function tests rather than an obstructive pattern as seen with asthma.

Western red cedar-induced asthma in sawmill workers seems like allergic asthma with features of (1) a latent period, (2) affecting less than 2% of workers, and (3) a late or biphasic pulmonary reaction on inhalation challenges. Bronchial biopsy studies in patients with Western red cedar asthma, however, reveal activated T lymphocytes [10]. Skin tests with red cedar extract have not been useful and specific IgE to Western red cedar combined with human albumin has been found in 30% of affected workers. It is likely that both immunologic and nonimmunologic mechanisms are involved in the disease [11].

Irrespective of the cause of immunologic asthma, the pathologic changes that are observed in patient's airways with occupational asthma are the same. These same changes are seen in nonoccupational asthma. The changes observed in *RADS* are slightly different and include denuded mucosa with

Table 1
Representative causes of occupational asthma

Occupation/industry	Source exposure	Causal agent
Animal handlers		
Veterinarians, laboratory workers, breeders, farmers, hunters	Guinea pigs, rats, mice, rabbits, cats, dogs, horses, hamster, cattle, hogs, sheep, goats, deer, bats	Urine protein, dander, excreta, serum
Bird breeders	Nearly all avian species	Feather bloom/droppings/dust/serum
Poultry workers	Arthropods Fungal protein	Mealworm, Northern fowl mite <i>Alternaria</i> , <i>Aspergillus</i>
Beauticians	Amines ^a	Diamine, ethanolamines, tetramines
Detergent industry workers	Enzymes in laundry detergent	<i>Bacillus subtilis</i> , protease, amylase, cellulase
Entomologists, beekeepers, Laboratory workers, sericulturist	Arthropod wings and body parts	Moths, cockroach, river fly, fruit fly, locust, meal worm, screw worm, grain weevil, sheep blowfly, cricket, honeybee body dust, house fly
Farmers, grain workers or handlers, agricultural research	Arthropods Grain, cereals Mold, bacteria, or endotoxin Other contaminants in dust	Grain mites, meal worm Barley, lupine Rusts, smuts Pesticides, fertilizers, insecticides (organophosphates), silica dust, cellulose hair and spikes, mineral particles ^a
Wine growers, vineyards	Pollen	<i>Diplotaxis erucoides</i>
Florists	Plant pollens, fruits, seeds, leaves Moldy dirt	Sunflower, "Baby's breath," weeping fig Verticillium albo-atrum
Food processors		
Bakers	Eggs Enzymes Flour Flour contaminants	Egg protein Alpha-amylase Wheat, buckwheat, rye, soy, gluten Grain storage mite, grain weevil, dough improvers, mold
Coffee, tea, or castor bean workers	Green coffee, tea, or castor bean dust or oil	Bean antigen
Seafood processing	Snow crab	Crab, prawn, shrimp, mother-of-pearl
Oyster farmers	Hoya (sea-squirt)	Oyster parasite

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Table 1 (continued)

Occupation/industry	Source exposure	Causal agent
Fish processing	Various fish species (eg, trout)	Fish protein in stream or water vapor
Cheese processing	Cheese workers	<i>Penicillium caseii</i> mold
Tobacco manufacturer	Tobacco	Tobacco leaf
	Gum manufacturer	Vegetable gum
Food or beverage processing	Meat tenderizer, beer treatment	Papain, chymopapain
Hair dresser	Bleaching agents	Persulfate salts ^a
	Hair dyes	Henna
	Irritants	Lacquer
Manufacturing		
Plywood particle makers		Formaldehyde, plexiglass dust, styrene
Meatwrappers		Polyvinyl chloride ^a
Metal refining		
Electroplating or printers	Metal plating factory	Chromium, nickel ^a
Solderers, locksmiths		Zinc, colophony ^a
Platinum refiners		Platinum salts ^{a,b}
Hardmetal grinders	Diamond polishers	Tungsten carbide, cobalt, vanadium ^a
Welders	Welding fumes	
Pharmaceutical workers, pharmacists, nurses	Antibiotics ^a	Penicillin, cephalosporin, isoniazid, tetracycline, spiramycin, sulfonamide
	Enzymes	Pancreatic extract, papain, pepsin, trypsin, chymopapain
	Laxative	Psyllium ^a
	Herbal agents	Ginseng, Chunkung, Banha, Sanyak
	Other HMW medications	Penicillamine, methyldopa, hydralazine, cimetidine
	Other LMW compounds	Ipecac, salbutamol, formaldehyde, amprolium
	Sterilizing agents	Chloramines, hexachlorophene ^a
	Vegetable gums (historically in printers)	Gum Arabic, gum acacia, tragacanth, karaya
Physicians, nurses, technicians	Powdered examination gloves	Latex
	Organic dyes and inks for ECGs ^a	
Paint and adhesive industry	Paint	polyurethane
Spray painters or foam makers	Paint, lacquer, adhesive, foam	Isocyanates (TDI, MDI, HDI) ^a
Plastic workers		
Epoxy resin workers	Acid anhydrides ^{a,b}	Phthalic, trimellitic, tetrachlorophthalic, Adipic acid
	Acrylates (acrylic)	Methacrylate, cyanoacrylates
Tanning Industry	Chromium salts	

Table 1 (continued)

Occupation/industry	Source exposure	Causal agent
Textile Industry	Cotton, flax, soft hemp Organic dyes	Plant proteins and endotoxin
Wood workers, carpenters, saw mill workers, forestry, loggers, construction workers	Western red cedar	Plicatic acid ^a
	Other woods ^a	Antiaris, Oak, Iroko, Redwood, Mahogany, Walnut, Ash
	Insects	Tussock moth

^a Low molecular weight.

^b IgE-dependent mechanism for a LMW agent.

Abbreviations: HDI, hexamethyl diisocyanate; HMW, high molecular weight; LMW, low molecular weight; MDI, diphenylmethane diisocyanate; TDI, toluene diisocyanate.

fibrinous and hemorrhagic exudates observed in the submucosa. Specific antibodies are not consistently identified or if present may merely be a marker of exposure rather than playing a pivotal role in the disease process.

Risk factors

Any individual who develops asthma during his or her working life should be assessed for occupational asthma. A previous history of asthma may be aggravated by workplace exposures through de novo sensitization or irritant factors. Several risk factors have been identified for developing occupational asthma.

The specific agent itself can pose increased risk. Exposure to platinum salts, which are highly potent sensitizing agents, can affect a large percentage of workers [27]. For some agents (eg, cedar, flour, and colophony) there is a dose-response relationship between the degree of exposure and development of asthma.

The observation that only a relatively small percentage of workers who are exposed to the same work environment develop occupational asthma suggests that host factors are involved. Currently, significant work is being performed on whole-genome screens for asthma and atopy. Chromosomal studies have identified several candidate genes on the long or short arms of chromosomes 5, 6, 7, 11, 12, and 14 that may be associated with various asthma phenotypes including IgE; β_2 -adrenergic receptor gene; airway hyperresponsiveness or cytokines associated with the inflammation of asthma or atopy including interleukin-3, -4, -5, -9, -12 beta chain, -13; and granulocyte-macrophage colony-stimulating factor [12]. No single genotype has been identified to explain the development of asthma.

For HMW agents the most important risk factors are believed to be the presence of atopy (allergic disease predisposition). Individuals with a family

or personal history of asthma, allergic rhinitis, or eczema are prone to develop IgE-mediated sensitivity to environmental agents [26]. This may be particularly relevant for industries where HMW compounds are used and asthma is IgE mediated, although this does not always hold true. Symptoms of rhinitis and conjunctivitis may precede the development of occupational asthma for HMW agents, such as occurs in laboratory animal workers [13]. The degree of risk in occupational asthma is unclear because many are case reports without known atopic status, the criteria for atopy in epidemiologic studies varies, and as in any occupational disease there is the potential for self-selection bias and influence of company hiring policies.

Cigarette smoking has not been linked consistently with the development of occupational asthma, and some studies of isocyanate asthma or Western red cedar asthma suggest that these agents may confer a degree of protection through unknown mechanisms.

The presence of nonspecific bronchial hyperresponsiveness as measured by methacholine, histamine, hyperventilation, cold air, or exercise pulmonary function challenge is characteristic of patients with asthma. It also occurs, however, in nearly 50% of individuals with seasonal allergic rhinitis, in some patients with bronchitis, transiently in a small percentage of those who receive the influenza vaccine, and in a small percentage of normal individuals. It is unclear if bronchial hyperresponsiveness is a risk factor for developing occupational asthma.

Causes of occupational asthma

There are literally hundreds of causes of occupational asthma stemming from a wide variety of work environments. Reports include epidemic outbreaks to single case reports. Many of these are outlined in Table 1. This table has been subdivided into occupations, realizing that both HMW (>3 kd) and LMW (<1 kd) agents can be found in the same environment.

Plants are probably the most common source of occupational allergens, available in many forms as dusts from woods; pollens; cereal flour or grains; beans (coffee or castor); latex; plant food; and food processing of herbs, seeds, or fruits and enzymes. Plicatic acid (a nonvolatile, water-soluble component) has been identified as the substance responsible for patient's developing asthma when working with Western red cedar wood.

Animal proteins including dander, excrement, secretions, and serum from a wide assortment of mammals, seafood, and poultry have been reported. Enzymes, gums, and fungal protein dust exposure encompass a wide range of occupations. Pharmaceuticals, chemicals (organic and inorganic), metals, and polymers represent additional categories of triggers for occupational asthma. Isocyanates are LMW chemicals used to harden polyurethane paint (auto and marine) and to create foam insulation. Diphenylmethane diisocyanate serves the same purpose as toluene diisocyanate but is less volatile

than toluene diisocyanate, decreasing the inhalation risk during an accidental spill. Colophony is causative in those individuals working with solder flux.

Because new products are being used for various purposes, cases of asthma are likely to continue to be identified. Recent case reports of occupational asthma include two wine growers with asthma triggered by the pollinating Crucifera plant *Diplotaxis erucooides* (wall rocket) present in vineyards [14]; agricultural researchers working with lupine seed flour, which is a legume related to peanuts [15]; and a pharmacist experiencing symptoms while chopping Oriental herbs [16].

Cases of occupational asthma may present with an index case and on further evaluation of workers, identify others who are affected. Detergent factories where powdered protease enzymes are manufactured have long been implicated in occupational asthma and despite encapsulation of enzymes and other controls to reduce airborne exposure, outbreaks continue to occur even in modern plants [7].

Nonspecific pulmonary irritants can be classified as water-soluble gases, nonsoluble gases, and metals or inorganic complexes [17]. These are considered nonspecific because they can have similar effects on all exposed people. High concentrations of water-soluble vapor or fumes can overwhelm the defense mechanisms of the pulmonary system resulting in immediate symptoms. Common examples include ammonia, chlorine, formaldehyde, and acids. The resulting condition called RADS occurs after single or multiple high-level exposures in individuals without previous asthma or respiratory illness [24]. Persistent low-level exposure may also result in a RADS presentation. Symptoms can persist for mean duration of 3 years and nonspecific bronchial hyperresponsiveness is persistent, but not necessarily lifelong. Water-insoluble agents produce symptoms several hours after exposure. Examples of these agents include ozone, phosgene, and nitrogen oxides. Inorganic complexes occur as vapors, fumes, or particulates and may trigger various airway disorders ranging from transient cough to pulmonary edema and adult respiratory distress syndrome.

Diagnosis

An early and accurate diagnosis of occupational asthma is of primary importance to provide the best outcome and prevent chronic irreversible lung damage. Key components of the evaluation are found in Box 1. The primary care physician or physician affiliated with the plant or factory has the greatest opportunity to diagnose occupational asthma. Early in the process of occupational asthma the work-related pattern may be apparent, as opposed to late in the process when persistent asthma is the presenting sign.

The diagnosis of occupational asthma rests on two major fundamental findings: (1) establishing the diagnosis of asthma, and (2) determining

Box 1. Diagnostic Evaluation of Occupational Asthma

1. History (see Box 2)
 - Symptoms, onset, triggers
 - Smoking history
 - Previous history of asthma
 - Other conditions: allergic rhinitis, sinusitis, cardiac disease, anxiety
 - Occupational history: job description, exposures, MSDS
 - Other exposure: hobbies
2. Physical Examination
 - Normal
 - Rhinitis, conjunctivitis
 - Wheezing, barrel chest
 - Clubbing
 - Rash
3. Chest Radiographs
 - Normal
 - Asthma: hyperinflation, bronchial wall thickening, flat diagrams, atelectasis
 - Evaluate for other entities in the differential diagnosis
4. Pulmonary Function Tests (PFT)
 - Spirometry (minimum)
 - Baseline
 - Response to β 2-agonist bronchodilator
 - Cross-shift^a (eg, pre- and post-shift measurements)
 - Complete PFTs
 - Spirometry, lung volumes, diffusion capacity, pulse oximetry
 - Peak flow measurements
 - Morning, workplace, and evening
 - Cross-shift^a
5. Inhalation Challenge Test
 - Non-specific bronchial hyperresponsiveness
 - Methacholine, histamine, cold air, exercise challenge
 - Worksite Challenge
 - Specific agent challenge test
6. Immunologic Tests
 - Allergy skin tests (for HMW agents)
 - In vitro tests for specific IgE
 - RAST^b
 - ELISA^c

^a Not helpful in delayed onset asthma symptoms (LMW compounds).

^b RAST Radioallergosorbent Test.

^c ELISA Enzyme-linked immunosorbent assay.

whether the asthma is caused or triggered by the workplace or by alternative nonoccupational exposures.

History

Although the most important aspect is a detailed and comprehensive history including occupation and hobbies, inaccurate conclusions easily can be drawn. Although many history questionnaire templates are available, the goals in collecting the occupational history are outlined in Box 2 and include the following: (1) to generate a list of present and past jobs, especially those that coincide with the onset of asthma symptoms; (2) to outline work duties and exposures at each of those jobs; and (3) to assess the probability that the asthma and the workplace are linked. Realizing that there are a number of high-risk professions and high-risk exposures, the physician can be armed with knowledge of these professions and exposures. Federal regulations mandate that material data safety sheets (MSDS) be made available to workers who are exposed to potentially hazardous materials. MSDS provide information on chemical composition, synonyms, physical and chemical composition and toxicity, and health risks. With the patient's permission, the physician can contact the employer if the patient is unable to supply sufficient information.

General patient evaluation

A thorough general evaluation including physical examination to assess for other health conditions should be accomplished. The symptoms of occupational asthma are no different from nonoccupational asthma and range from isolated cough, wheeze, dyspnea, or chest tightness to any combination of these. The physical examination is unfortunately not helpful in differentiating occupational asthma from nonoccupational asthma and may be normal. The record should document the presence or absence of findings, such as wheezing, congestion, rales or crackles, prolonged expiratory phase, poor air excursion, clubbing, or cyanosis. Physical findings may be helpful in identifying other conditions in the differential diagnosis. Specifically, the presence of cardiac disease should be assessed because this may be the origin of the chest complaints. A family history of asthma is similar in those with both occupational and nonoccupational asthma.

Radiography

A standard two-view chest radiograph is essential particularly in cases where there has been prolonged exposure to dusts or chemicals. In acute-onset occupational lung disease, the chest radiograph may distinguish between alveolar disease and obstructive airway disease, although findings consistent with asthma do not help confirm the causal agent. Similarly, a normal chest radiograph does not exclude the diagnosis of asthma.

Box 2. Specific Occupational History

Current occupation/job title and specific work activities

(Secondary occupation/job)

Shift, hours per day, duration at that job

All known exposures: individual chemicals or substances

Forms of the substance: gases, fumes, vapors, dusts, aerosols

Detailed symptoms:

General: headache, fatigue, malaise, weight loss, appetite change, fever

Ocular, nasal or skin irritation

Upper respiratory symptoms: throat tightness, choking, difficulty with inspiration

Pulmonary complaints: frequency, severity, progressing/plateaued/regressing

Co-existing respiratory infection

Temporal relationship of symptoms to workplace

Symptoms: nighttime, holidays, weekends, vacations, leaves of absence

Similar problems in other workers

Protective equipment used

Gowns, hoods, gloves (latex/non-latex, powdered), masks, respirators

Worksite evaluation

General engineering, HVAC^a, fans, exhaust hoods, spills

All work activities in same building:

Recent remodeling, building, changes in chemical use

Data on air/fluid/soil sampling, medical monitoring, safety education

Nearby factories

All past work activities

Same information as above including toxic agents

Non-work related activities:

Hobbies (gardening, pets, animal handling, painting,

Habits: smoking, drug use (cannabis)

Past medical history

Cardiac, gastrointestinal or pulmonary disease

Prescription medications

Beta-blockers, aspirin/NSAIDs^b, ACE inhibitors^c

^a HVAC: heating, ventilation, air conditioning.

^b NSAID: Nonsteroidal anti-inflammatory drug.

^c ACE: Angiotensin-converting enzyme inhibitors.

Unfortunately, there is poor correlation between early radiographic findings and pulmonary function or symptomatology.

Pulmonary function testing

It is imperative to document any pulmonary dysfunction. If discovered, then further evaluation by pulmonary and allergy specialists familiar with occupational diseases is recommended. Although there are many tests of pulmonary function, the one best suited for occupational asthma is spirometry. It is reliable, inexpensive, rapid, portable, noninvasive, simple to administer, and safe. When properly performed and interpreted, it is sensitive and specific. The measurements obtained from a forced expiratory maneuver include forced vital capacity (FVC); forced expiratory volume in 1 second (FEV_1); ratio of FEV_1 to FVC expressed as a percentage; average forced expiratory flow over mid range of the expiratory curve ($FEF_{25-75\%}$); and peak expiratory flow, compared with normal values (adjusted for age, gender, height, and race). When combined with bronchodilator response (eg, administering albuterol either by nebulization or metered dose inhaler, then repeat spirometry) reversible airways obstruction can be documented.

The diagnosis of asthma can be established by either demonstrating an improvement in lung function (FEV_1) by 12% to 15% or through use of a nonspecific challenge (cold air or exercise) or pharmacologic challenge (methacholine or histamine) with a decrease in FEV_1 by 20%. On occasion the methacholine challenge is normal unless performed on the day of exposure to the workplace.

Challenge testing

One can establish the workplace as the relevant environment in several manners if the history suggests an occupational cause but no known sensitizing agent is present, the inducing agent is unknown, or bronchial hyperreactivity cannot be determined by nonspecific testing as noted previously. Before this approach is undertaken, the worker should take a leave of absence long enough to be asymptomatic and permission should be obtained from the employer. Monitoring peak flow measurements immediately before, during, and after a work shift is known as *cross-shift measurements*. The usefulness of this approach is hampered by the effort the individual gives during the maneuver [25]. Accurate peak flows or FEV_1 measurements can demonstrate decreases in lung function in several different patterns. A HMW agent may produce an early or immediate response with decreases in lung function within an hour of exposure with or without a late-phase response that occurs 4 to 12 hours later. LMW agents are associated with an isolated late response that could occur at home after leaving work, overlooked as being linked to the occupation. Early in the course of occupational asthma there is a typical pattern of symptoms and decreased lung function occurring at work and improving away from work,

on weekends, and on vacations. With continued exposure, however, this pattern can change to one consistent with persistent asthma symptoms and abnormal lung function. To complicate the diagnosis, asthma symptoms may be aggravated by nonspecific irritants away from work including smoke, fumes, cold air, exercise, or home or outdoor environmental allergens. Even if an occupational link is established, the specific agent in that workplace may be difficult to identify. False-negative workplace challenges can occur if the agent is not present on the day of challenge or is present in too low of a concentration to produce symptoms or lung function measurements. To summarize, the asthma pattern that can occur is early, late, dual, or persistent. The methacholine challenge reactions can disappear over time as healing occurs, especially in RADS.

Allergy skin testing and serology

Allergy skin testing or in vitro tests for IgE serology (radioallergosorbent test or ELISA) can be useful in ascertaining the atopic status of the individual and in identifying if the patient is sensitized to HMW allergens in the workplace. IgE serology is generally less sensitive and more expensive than allergy skin testing. A specialist familiar in the placement and interpretation of such tests best performs allergy skin testing. Unfortunately, LMW agents are typically not mediated by an IgE mechanism, rendering these tests unreliable. In an industrial exposure where multiple chemical compounds are encountered, skin testing with crude substances may lead to both false-positive (irritant reactions) and false-negative reactions. Furthermore, standardized skin testing reagents are not available for the special situations found in many industries. In cases of toluene diisocyanate-induced asthma, specific IgE to protein-hapten conjugates rather than the chemical agent alone can be identified. Routine laboratory studies are generally not helpful in assessing patients with occupational asthma. Complete blood counts and total serum IgE levels are typically normal.

Specific inhalation challenge testing

Some hospital pulmonary function laboratories or research laboratories may perform intentional specific inhalation challenges. These should only be done, however, under the direction of an experienced specialist who is trained in monitoring and treating severe asthma exacerbations. Unfortunately, the delivered dose and duration may be different than that encountered at the workplace and the possibility exists to produce ongoing symptoms. The choice of the proper agent and form (vapor, gas, particulate, fume, heated or not) is critical. Various parameters to monitor during a challenge include the standard measurements of spirometry and vital signs. Potential new markers to assess preinhalation and postinhalation challenge include blood eosinophils, serum tryptase, and eosinophil cationic protein levels [18].

Worksite evaluation

Despite the ability to gather information from the patient or MSDS, a site visit to the patient's worksite can be useful in identifying specific sources of exposure. The plant engineer who is most familiar with the details of the plant processes and operations can be helpful in pinpointing sources of exposure. With the cooperation of plant management, the assistance of an industrial hygienist can be invaluable in obtaining workplace data through a walk-through inspection and by obtaining (1) personal air samples, (2) air quality for irritants (CO and CO₂), (3) ventilation and air turnovers, and (4) fluid or soil samples for culture.

Therapeutic trial

A therapeutic trial with inhaled corticosteroids and β_2 -agonist bronchodilators can provide symptomatic relief for the patient while the evaluation process is in progress. If the probability is high that the worksite is contributing to respiratory symptoms, temporary removal of the worker from that area or the entire building is recommended.

Future techniques

New techniques that are being evaluated for use in the investigation of occupational asthma are exhaled nitric oxide and induced sputum analysis for eosinophils. Additional studies are required to assess their clinical usefulness.

Differential diagnosis

The most common and difficult diagnosis to differentiate from occupational asthma is nonoccupational asthma. Other occupational lung diseases that can be confused with occupational asthma are found in Box 3 and include hypersensitivity pneumonitis, occupational or industrial bronchitis, pneumoconioses, infectious diseases, and organic dust toxic syndromes. Work-related respiratory complaints without evidence of asthma include the so-called *sick building syndrome* and psychogenic disorders.

Features that differentiate hypersensitivity pneumonitis include dry cough and dyspnea especially with exertion without associated wheezing. Pulmonary function tests reveal a restrictive pattern with decrease in both FVC and FEV₁, although airway obstruction is not uncommon in chronic hypersensitivity pneumonitis. Patchy interstitial infiltrates characterize hypersensitivity pneumonitis. Typical occupations and hobbies include farming; bird breeding; machinists; plastic and chemical (isocyanates) industry; and mold-contaminated heating, ventilation, and air-conditioning systems.

Box 3. Differential Diagnosis of Occupational Asthma**Asthmatic Disorders**

Pre-existing asthma with irritant exposure

Work-related Non-asthmatic Disorders

Industrial bronchitis

Bronchiolitis obliterans

Adult Respiratory Distress Syndrome (ARDS)

Organic Dust Toxic Syndrome (ODTS)

“Metal fume fever”

“Silo Unloader’s Disease”

“Grain Fever”

“Animal house fever”

“Mill fever”

“Monday morning fever”

Pneumoconioses

Silicosis

Berylliosis

Building-Associated Illnesses

Hypersensitivity pneumonitis (extrinsic allergic alveolitis)

Pulmonary Infectious Disease

“Sick Building Syndrome”

Psychogenic Disorders

Paradoxical vocal cord dysfunction

Work-related Anxiety

Malingering

Non-Work-related Non-asthmatic Disorders

Unrelated lung disorder

Chronic Obstructive Pulmonary Disease (COPD)

Alpha-1 protease deficiency

Lung neoplasm

Hypersensitivity pneumonitis (home/hobby exposure)

Idiopathic pulmonary fibrosis

Cardiovascular Disease

Congestive heart failure

Pulmonary embolism

Gastroesophageal Reflux Disease (GERD)

Occupational bronchitis is not well characterized but affects the larger airways with symptoms of cough and sputum production. It is not associated with bronchial hyperresponsiveness or abnormal chest radiographs. The symptoms improve with avoidance of the offending agents.

Organic dust toxic syndromes are a heterogeneous group of lower respiratory disorders distinguished by transient cough and dyspnea not related

to specific sensitization or a latent period. They occur in most exposed individuals especially with high exposures. The trigger is believed to be toxins or organic gases. Pulmonary function is minimally affected and chest radiographs are normal. Typical occupations include farming and raising swine and poultry.

Chronic-onset diseases that are associated with prolonged (>15 years) high-dose inorganic dust exposure include silicosis, berylliosis, and various other pneumoconioses. These diseases typically lead to progressive fibrosis and a restrictive pattern rather than obstructive pattern in lung function. Typical occupations include mining, quarrying, stone cutting, foundries, brickyards, glassmaking, ceramics, and sandblasting.

A variety of infectious diseases have been associated with building-related respiratory disease that can mimic occupational exposures. These diseases tend to occur in epidemic fashion and include Pontiac fever, Q fever, and legionnaires' disease.

Paradoxical vocal cord dysfunction can complicate asthma, especially if factors at work escalate anxiety. A history of cigarette smoking is important because chronic obstructive pulmonary disease may be a factor in lower respiratory symptoms. The sick building syndrome, which is more accurately described as "building-related illness" is a clinical diagnosis believed to be caused by the accumulation of irritants within a building related to engineering changes that decrease fresh air intake. The symptoms can include difficulty breathing, but objective measures of airway obstruction or bronchial hyperresponsiveness are lacking. More common are subjective symptoms of fatigue, decreased attention span, headache, and sore throat.

Work-related illnesses can also be complicated by underlying anxiety-provoking issues and issues related to primary and secondary gain. Work-related injury has the extraordinary potential to be linked to compensation. Crowd behavior that results in mass hysteria can potentially be the result of identifying a trigger of occupational asthma.

Treatment

Avoidance

The primary goal of occupational asthma is avoidance of the offending trigger. Avoidance measures can be accomplished in many ways, some of which are better tolerated or easier to implement, but all are expensive. Personal respiratory protection using masks, hoods, or suits with hoods and a separate fresh air system is available. Adherence to these recommendations is problematic because of discomfort and heat. Enclosing processes that produce fumes or particulates can decrease exposure to the operator. Improving ventilation and frequency of air exchange can decrease the concentration of airborne agents. Substitution of one agent for a safer agent if one is available is an option. The change of location of the person's job effectively can

block exposure as long as heating, ventilation, and air-conditioning ductwork is separate. Occasionally, a change in occupation is necessary. Unfortunately, this is complex requiring retraining or relocation.

Pharmacologic management

The pharmacologic agents used in treating occupational asthma are no different from those used in treating nonoccupational asthma. Acute treatment is an adjunct to avoidance measures. The early addition of oral corticosteroids may facilitate the healing process, whereas regular use of inhaled corticosteroids may accelerate the improvement in bronchial hyperresponsiveness. Persistent asthma requires daily controller medications, whereas mild, intermittent asthma can be managed with intermittent use of β -agonist bronchodilators. High-dose specific allergen immunotherapy by subcutaneous injection does not have a role in therapy for occupational asthma except potentially in animal dander-induced asthma.

Prevention

After identification of the causal agent, prevention is a high priority in management to prevent an already affected employee from further exposure and prevent other employees from developing symptoms. A case of occupational asthma should serve as a sentinel event, prompting an evaluation of the workplace and other employees with similar exposure. Further employee evaluation termed *medical surveillance* may include a symptom questionnaire or survey, serologic surveys, chest radiographs, and lung function testing. Workplace changes that could decrease employee exposure include employee education; industrial hygiene measures; and engineering controls (eg, enclosure of various machining processes and changes to the heating, ventilation, and air conditioning systems). Additional monitoring of air or fluid levels of agents and sensitizers could help keep exposure levels below recommended levels. Personal respiratory protection as noted previously may be necessary for other exposed but asymptomatic personnel. In regard to laboratory animal allergy, special individually ventilated mice cages can substantially reduce animal allergen exposure [19].

Prognosis

The prognosis of individuals with occupational asthma is dependent on the following factors: (1) chemical and biologic nature of exposure, (2) latency between exposure and symptoms, (3) latency between onset of symptoms and removal, (4) degree of initial impairment in FEV₁, and (5) degree of bronchial hyperresponsiveness [20]. Once diagnosed, the potential clinical outcomes include complete resolution or persistent sensitization with intermittent or persistent asthma symptoms.

An extremely important factor is duration of symptoms because early diagnosis and avoidance of the offending trigger can significantly affect long-term outcome [21]. With early diagnosis and treatment, nearly 50% of patients have improvement in their symptoms, lung function, and bronchial hyperresponsiveness as measured by methacholine challenge. The presence of permanent bronchial hyperresponsiveness may be documented in 75% of workers even after removal from the causal agent [21]. Serial measurements of bronchial hyperresponsiveness as assessed by methacholine challenge are common practice at the author's institution. The specific environmental agent causing the asthma is also important in prognosis. Workers with Western red cedar asthma have an increased rate of persistent impairment of lung function and symptoms. For those sensitizing agents, once an individual has become sensitized, very small exposure levels can trigger an asthma attack.

In general, most patients achieve a healing plateau within 2 years after avoidance measures have been undertaken [22]. Five years after cessation of exposure, however, further improvement in lung function and even loss of bronchial hyperresponsiveness may be seen in a small percentage of workers. Unfortunately for some individuals, even after cessation of exposure, long-term prognosis may be poor with chronic symptoms and irreversible airway obstruction.

Impairment, disability, and compensation

Because of the nature of occupational asthma and the effect it has on an individual's ability to earn an income, these cases are frequently associated with medicolegal questions of degree of impairment; percent disability (either partial or permanent); and compensation. To answer these questions accurately, it is helpful to manage these patients within a multidisciplinary team familiar with the processes and intricacies that invariably arise in such situations. If a large plant or company is involved, the plant physician is an integral part in these matters and in screening and ongoing treatment issues.

Frequently, the language used in describing the extent of occupational asthma is confusing. The American Medical Association and American Thoracic Society Guidelines are the most common set of guidelines used today. The term *handicap* is used to signify the inability to perform a specific activity or function that the individual is incapable of performing. *Impairment* is defined as a medical condition resulting from a functional abnormality. The medical condition may be temporary or permanent and at the time of evaluation may be stable or unstable. Disability is the total effect of an impairment on a patient's life. A patient who is no longer able to do their specific work because of respiratory symptoms is totally disabled. Using these definitions, properly performed spirometry with emphasis on the FVC and FEV₁ can measure respiratory impairment, whereas disability requires a

number of assumptions. Important evidence includes the effect on daily activities, ability to perform the work, whether the disease is stabilized, likelihood that occupational demands will lead to further impairment, and the need for accommodations or restrictions. Unfortunately, the number and amount of medications necessary to control a patient's symptoms are not currently used as an indicator of severity.

Summary

Occupational asthma is a common yet all too frequently unnoticed form of adult asthma. Many agents can trigger disease by a variety of mechanisms, some of which are unknown. Awareness of high-risk occupations and knowledge that adults with persistent asthma may have an occupational trigger are vital in early identification and treatment of this population of patients where the stakes are high. Although the sensitivity and specificity of various tests are low, a multidimensional approach, which includes the cooperation of primary care physician, allergist-immunologist, pulmonologist, industrial hygienist, occupational medicine specialist, and industry (union and management), can lead to a successful outcome in a timely manner.

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