Chapter 17
Occupational Asthma

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Definition of Occupational Asthma

Occupational asthma has been defined as "a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace." Two types of OA need to be distinguished based on the presence of a latency period (includes most high molecular weight agents and some low molecular weight agents) or absence of a latency period (includes irritant-induced asthma aka reactive airways dysfunction syndrome). High molecular weight (HMW) agents refer to plant or animal proteins >1,000 Kd in size such as natural rubber latex, enzymes, or laboratory animal allergens. Low molecular weight (LMW) agents refer to chemicals <1000 Kd in size that usually require conjugation with endogenous proteins to form a complete hapten capable of eliciting an immunogenic response. Examples include isocyanates, acid anhydrides, and metallic salts. It is important to emphasize that preexisting asthma does not preclude a diagnosis of OA. The term "work-exacerbated asthma" has been recommended for patients with this presentation.

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History and Epidemiology

The first reference to asthma in workers was cited by Hippocrates (460–370 BC) in reference to metal workers, tailors, horsemen, farmhands, and fishermen. Throughout history, physicians have increasingly recognized the relationship between asthma and a variety of occupations.

The incidence of OA is difficult to estimate as there are significant differences between countries, ranging between 10 and 114 per million per year. These differences are largely due to methodological differences in calculating incidence and the types of occupations and employment opportunities in each country. The Sentinel Event Notification System for Occupational Risks (SENSOR) was developed in several states within the United States in the 1980s to encourage reporting of OA cases by physicians and to put them in contact with public health agencies responsible for investigating high-risk workplaces. This program was successful at increasing awareness among physicians about OA; however, as with other notification systems, underreporting was a problem. Other countries have developed voluntary reporting registries to identify an ongoing incidence and prevalence of OA with varying degrees of success. Asthma cases being evaluated for work-related medicolegal benefits have been another source for estimating the incidence of OA.

Overall, it has been estimated that 5–20 % of all new diagnoses of asthma are occupationally related. Over 250 agents in the workplace have now been associated with causing OA. Cross-sectional studies have provided much of the prevalence data available for many of these agents known to cause OA. The prevalence of OA varies between occupations. For example, studies have found the prevalence of OA among laboratory animal workers is approximately 20 %, whereas western red cedar asthma occurs in approximately 5 % of workers. The prevalence of OA has been estimated to occur in 7–9 % of bakers for baker's asthma, 5–10 % of isocyanate-exposed workers, 20–50 % of platinum-exposed workers, and in up to 60 % of enzyme-exposed workers.

The prevalence for OA within a specific occupation depends on many factors including environmental conditions within the plant, exposure levels, and the number of exposed workers. For example, at first glance, it might appear that isocyanate-exposed workers have a lower prevalence of OA compared to platinum-exposed workers. However, the absolute number of workers exposed to isocyanates (>100,000) each year results in a greater absolute number of workers who develop isocyanate-induced OA compared to platinum-exposed workers.

Unfortunately, cross-sectional studies can underestimate the prevalence of OA due to the "healthy worker effect." This phenomenon occurs as the result of symptomatic workers leaving the workplace because of illness which results in a misleading healthier workforce. Therefore, in order to obtain more accurate prevalence statistics and information about the causes, risk factors, and natural course of OA, surveillance programs have been established in developed countries including the United Kingdom, the United States, and Finland. The "SWORD" (Surveillance of Work-Related and Occupational Respiratory Disease) program established in the

United Kingdom involves voluntary reporting of occupational illnesses from a variety of industries by pulmonologists and occupational medicine physicians. This program has already yielded useful prevalence data due to the excellent response rate from participating physicians. Thus far, SWORD has identified OA as the most frequently reported occupational respiratory illness and isocyanates as the most common specific cause of OA. As mentioned, the "SENSOR" (Sentinel Health Notification System for Occupational Risks) program established in the United States has not been as successful in obtaining useful epidemiological data due to a poor response rate from participating physicians. This is in contrast to Finland's program, which has already compiled enough data to estimate the country's yearly incidence of OA and hypersensitivity pneumonitis. Currently immunosurveillance programs implemented by companies manufacturing potentially sensitizing chemicals and enzymes are ongoing and have proven very effective at reducing and/or preventing occupational respiratory diseases.

Pathogenesis

Our understanding of asthma has been greatly enhanced with the advent of bronchoscopy, bronchoalveolar lavage, and bronchial biopsies. The pathogenic features of OA are similar to what has been observed in non-OA patients. In general, lung biopsies of patients with OA demonstrate increased numbers of inflammatory cells with a predominance of eosinophils and lymphocytes, increased intercellular spaces between epithelial cells, and thickening of the reticular basement membrane due to deposition of collagen (types I, III, and V). Interestingly, the degree of reticular basement membrane thickening has been demonstrated to differ between different forms of OA. For example, workers with reactive airways dysfunction syndrome (RADS) have thickening that can reach 30–40 μm compared to 6–15 μm in workers with diisocyanate asthma and 3–8 μm in normal subjects. Airway inflammation associated with OA involves similar bioactive mediators and proinflammatory cytokines identified in non-OA. Certain causes of work-related lower respiratory symptoms have been reported to manifest as eosinophilic bronchitis, characterized as a chronic cough with sputum eosinophilia in the absence of bronchial airway hyperresponsiveness. For example, natural rubber latex, mushroom spores, acrylates, and epoxy resins have been reported to present as eosinophilic bronchitis. Occupational asthma manifesting as neutrophilic inflammation is less common but has been reported with some low molecular weight agents. For non-OA the presence of neutrophils is believed to be a marker of severity, but their role in different causes of OA is still unclear.

Patients with OA can exhibit the inflammatory phases of asthma similar to non-OA. However, some forms of OA are more commonly associated with either the early airway response (EAR), the late airway response (LAR), or a dual airway response (DAR). For example, whereas an EAR may be more characteristic of high molecular weight (HMW) agents, an LAR or DAR may be more commonly seen in

workers with isocyanate-induced OA. Therefore, it is important for the clinician to be familiar with these different disease presentations to avoid missing a diagnosis of OA because symptoms by history begin after leaving the workplace.

Mechanisms

In general, many HMW and LMW agents known to cause OA involve Th2 proinflammatory cytokines characteristic of IgE-mediated allergic asthma. For example, enzymes commonly used in the detergent manufacturing industry are proteins that have been well documented to cause OA through IgE-mediated mechanism. Acid anhydrides are examples of LMW agents known to cause IgE-mediated OA. However, some LMW chemicals (plicatic acid and diisocyanates) cause OA in nonatopic workers through non-IgE-mediated mechanisms. The mechanism(s) by which these agents cause OA is unknown. The mechanism(s) for irritant-induced asthma (aka reactive airways dysfunction syndrome or RADS) also remains elusive. It is believed chronic inflammatory changes occur in these workers as the result of toxic injury to bronchial epithelial cells leading to loss of epithelial-derived relaxing factors combined with neurogenic inflammation and release of bioactive mediators and proinflammatory cytokines by nonspecific activation of mast cells. Ongoing research using a variety of animal models is trying to further elucidate the role of innate and adaptive immune responses in causing a variety of non-IgE-mediated forms of OA.

Genetics

Several studies have now reported potential and important genetic associations in workers who develop OA. For example, workers with acid anhydride OA have been shown to express the class II HLA molecule, DQB1*501, while this same molecule may be protective against developing OA from isocyanates or plicatic acid. Furthermore, the HLA-DRB1*07 phenotype was more commonly expressed in laboratory animal handlers sensitized to rat lipocalin allergens. Glutathione S-transferase polymorphisms, important for protecting cells from reactive oxygen species, have been postulated to protect workers exposed to isocyanates from developing OA and are also believed to play a protective role against developing non-OA from ozone and diesel exhaust particulate exposures. Finally, N-acetyltransferase genotypes may also be important in OA as recent studies have found that individuals with a slow acetylator genotype had a 7.8-fold risk of developing toluene diisocyanate-induced (TDI) asthma. A variety of other candidate gene polymorphisms found to be associated with non-OA phenotypes have also been investigated to a lesser extent in OA such as IL-4Rα S478P and IL-4-589. In a more recent study, subjects with diisocyanate asthma were found to have elevated levels of

IFN-γ promoter methylation than those who did not have diisocyanate asthma. However, the role of increased methylation in diisocyanate asthma remains unclear at this time.

Diagnosis

History

The criteria for defining occupational asthma proposed by the American College of Chest Physicians are summarized in Table 17.1. The diagnosis of OA requires a detailed and comprehensive history (Table 17.2). An inadequate history can often delay the diagnosis of OA for months or years. To prevent omission of important historical data, administration of a physician-directed history in conjunction with a structured questionnaire is recommended. The occupational history should elicit comprehensive demographic data about the worker; present and past employment history; the nature, duration, and temporal pattern of symptoms; and finally, any potential risk factors for OA. It is essential that the physician be familiar with most of the known causative HMW and LMW agents of OA and methodologies used for diagnosis (Table 17.3).

Table 17.1 Criteria for defining occupational asthma proposed by the American College of Chest Physicians

A. Diagnosis of asthma
B. Onset of symptoms after entering the workplace
C. Association between symptoms of asthma and work
D. One or more of the following criteria:
1. Workplace exposure to an agent or process known to give rise to occupational asthma
2. Significant work-related changes in FEV1 or peak expiratory flow rate
3. Significant work-related changes in nonspecific airway responsiveness
4. Positive response to specific inhalation challenge tests with an agent to which the patient is exposed at work
5. Onset of asthma with a clear association with a symptomatic exposure to an irritant agent in the workplace RADS
Requirements
Occupational asthma:
Surveillance case definition: A + B + C + D1 or D2 or D3 or D4 or D5
Medical case definition: A + B + C + D2 or D3 or D4 or D5
Likely occupational asthma: A + B + C + D1
Work-aggravated asthma: A + C (i.e., the subject was symptomatic or required medication before and had an increase in symptoms or medication requirement after entering a new occupational exposure setting)

RADS reactive airways dysfunction syndrome, *FEV1* forced expiratory volume in 1 s

Table 17.2 Key elements of the occupational history in the evaluation of occupational asthma

I. Demographic information
A. Identification and address
B. Personal data including sex, race, and age
C. Educational background with quantitation of the number of school years completed
II. Employment history
A. Current department and job description including dates begun, interrupted, and ended
B. List of all other work processes and substances used in the employee's work environment. A schematic diagram of the workplace is helpful to identify indirect exposure to substances emanating from adjacent work stations
C. List of prior jobs at current workplace with description of job, duration, and identification of material used
D. Work history describing employment preceding current workplace. Job descriptions and exposure history must be included
III. Symptoms
A. Categories:
1. Chest tightness, wheezing, cough, shortness of breath
2. Nasal rhinorrhea, sneezing, lacrimation, ocular itching
3. Systemic symptoms such as fever, arthralgias, and myalgias
B. Duration should be quantitated
C. Duration of employment at current job prior to onset of symptoms
D. Identify temporal pattern of symptoms in relationship to work
1. Immediate onset beginning at work with resolution soon after coming home
2. Delayed onset beginning 4–12 h after starting work or after coming home
3. Immediate onset followed by recovery with symptoms recurring 4–12 h after initial exposure to suspect agent at work
E. Improvement away from work
IV. Identify potential risk factors
A. Obtain a smoking history along with current smoking status and quantitate number of pack years
B. Asthmatic symptoms preceding current work exposure
C. Atopic status
1. Identify consistent history of seasonal nasal or ocular symptoms
2. Family history of atopic disease
3. Confirmation by epicutaneous testing to a panel of common aeroallergens
D. History of accidental exposures to substances such as heated fumes or chemical spills

Although questionnaires are essential, they have limitations. Occupational questionnaires are sensitive but not specific and, therefore, cannot be used to make a diagnosis of OA without confirmatory objective testing. The poor correlation between a history of OA and OA confirmed by specific challenge testing emphasizes the limitations of the medical history. While several itemized questionnaires have been utilized for obtaining an occupational history by different investigators, there is as yet no standardized instrument available for this purpose. However, several groups of experienced investigators have developed questionnaires, which have been validated by repeated use in cross-sectional or longitudinal studies. Recently,

Table 17.3 Etiologic agents of occupational asthma and reported immunologic tests

Agent	In vivo	In vitro
Azodicarbonamide	Prick tests with 0.1, 1, and 5 % azodicarbonamide	Not done
Baby's breath	Intradermal titration testing	RAST/histamine release
Bacillus subtilis enzymes	Prick tests with 0.05, 0.5, 5, and 10 mg/ml	RAST/radial immunodiffusion
Buckwheat flour	Prick test with 10 mg/ml	Reverse enzyme immunoassay/histamine release
Carmine dye	Skin test with coccus cactus	RAST to dyes
Castor bean	Prick test with 1:100 extract	Not done
Chloramine-T, halazone	Scratch test at 10^{-5} dilution	Not done
Chromate	Prick test at 10, 5, 1, and 0.1 mg/ml $Cr_2(SO_4)_3$	RAST to HSA-chromium sulfate
Cobalt	Patch tests	RAST to HSA-cobalt sulfate
Coffee bean	Intradermal titration to coffee bean extract	RAST to coffee bean extract
Diazonium tetrafluoroborate (DTFB)	Not done	RAST to HSA-DTFB
Dimethylethanolamine	Prick tests to dimethylethanolamine undiluted at 1:10, 1:100, and 1:1000	Not done
Douglas-fir tussock moth	Cutaneous tests with 1:25 extract	Histamine release
Dyes, textiles	Prick or scratch tests to dyes at 10 mg/ml in 50 % glycerine	HSA-dye
Egg proteins	Prick tests with 1:10 w/v egg white, egg yolk, whole egg; prick tests to 10 mg/ml egg white fractions	RAST to egg proteins
Ethylenediamine	Intracutaneous test to 1:100 ethylenediamine	Not done
Furan binder	Not done	RAST to catalyst, sand, and furfuryl alcohol
Garlic	Prick test titrations beginning at 10^{-5} garlic extract	PTRIA for IgE against garlic extract
Grain dust, grain dust mite	Prick and intracutaneous tests with grain dust and grain mite	Not done
Grain weevil	Skin test to weevil extract	Not done
Gum acacia	Skin tests with gum arabic	Not done
Guar gum	Prick tests with 1 mg/ml guar gum	RAST with guar gum
Hexamethylene diisocyanate (HDI)	Prick tests to HSA-HDI	ELISA to HSA-HDI
Hexahydrophthalic anhydride (HHPA)	Not done	RAST to HSA-HHPA
Hog trypsin	Skin test to trypsin	Histamine release
Laboratory animals	Skin tests with serum and urine extracts from animals	ELISA

(continued)

Table 17.3 (continued)

Agent	In vivo	In vitro
Latex	Prick test using low ammonia latex solution	Not done
Locusts	Prick tests with locust extract at 0.1, 1, and 10 mg/ml	ELISA
Mealworm	Prick test titration beginning at 1:20 w/v Tenebrio molitor (TM) extract	RAST to TM extract
Diphenylmethane diisocyanate (MDI)	Prick test with 5 mg/ml HSA-MDI; intradermal test with 1 μg/ml and 10 μg/ml	ELISA to HSA-MDI
Mushroom	Prick test with mushroom extract	Not done
Nickel	Prick tests with $NiSO_4$ at 100, 10, 5, 1, and 0.1 mg/ml	RAST to HSA-$NiSO_4$
Papain	Skin test with papain at 1.25–20 mg/ml	RAST to papain
Pancreatic extract	Prick tests with 1:100 and 1:1,000 extracts	Not done
Penicillin	Prick tests to ampicillin at 10^{-3} to 10^{-2} mol/l, benzylpenicilloyl polylysine at 10^{-6} mol/l and minor determinants at 10^{-2} mol/l	Not done
Penicillamine	Prick tests with penicillamine, major and minor penicillin determinants at 0.01, 0.1, and 1 mg/ml	Not done
Phthalic anhydride (PA) and tetrachlorophthalic anhydride (TCPA)	Prick and intradermal tests to HSA-PA and HSA-TCPA	ELISA; PTRIA to HSA-PA only
Platinum	Prick tests with complex platinum salts from 10^{-3} to 10^{-11} g/ml	RAST to $(NH_4)_2PtCl_2$, RAST to HSA-platinum, and histamine release
Poultry mites	Skin tests with 1:10 w/v Northern fowl mite (NFM)	RAST to NFM
Protease bromelain	Prick test with bromelain at 10 mg/ml	RAST to bromelain
Redwood	Prick test to redwood sawdust extract	Not done
Spiramycin	Prick tests with 10 and 100 mg/ml spiramycin	Not done
Tobacco	Skin tests with green tobacco extract 10 mg/ml	RAST with green tobacco extract
Toluene diisocyanate (TDI)	Prick test to 5 mg/ml HSA-TDI	RAST and ELISA to HSA-TDI, histamine release
Trimellitic anhydride (TMA)	Prick tests to 3.4 mg/ml HSA-TMA and TMA in acetone	PTRIA with HSA-TMA
Western red cedar (WRC)	Prick tests with 25 mg/ml WRC extract; intracutaneous testing with 2.5 mg/ml WRC	Not done
Wheat flour	Prick tests with 10 % w/v extract	RAST to wheat flour and wheat flour components

validated questionnaires are now available to help primary care physicians recognize a case of work-related asthma.

The basic components of a structured occupational questionnaire include an employment history and medical history. The employment history should ascertain information regarding the individual's work process including all jobs that could be related to specific exposures, work processes in adjacent areas, work shift hours, and previous jobs where the worker may have been exposed to similar or identical agents. The medical history should determine any relationship of symptoms experienced before, during, or after work to a specific exposure in the workplace; duration of symptoms after leaving the workplace; improvement of symptoms on weekends or vacations; associated upper respiratory and dermatologic symptoms; systemic symptoms such as fever, chills, or temperature; smoking history; preexisting allergy/asthma history; and previous chemical spill exposure.

The classic presentation of a worker with OA often consists of symptoms which begin at work and resolve or improve either shortly after leaving the workplace at night, during weekends, or while on vacation. However, a worker with OA may not improve away from the workplace because of chronic airway inflammation as a result of persistent workplace exposure to an agent for months or years after the initial onset of symptoms. In addition, patients with the reactive airways dysfunction syndrome (RADS) typically do not improve away from work. Therefore, the diagnosis of OA should not be overlooked because of the apparent lack of correlation of symptoms to workplace exposure.

Material Safety Data Sheet (MSDS) are an essential part of the occupational history. They provide valuable information regarding generic chemical names and specific constituents of raw materials being used in the workplace. They also provide standard information about threshold limit values (TLVs) and permissible exposure levels (PELs) of potentially toxic and/or sensitizing agents. When available, assistance from industrial hygienists or safety officers familiar with the workplace and the worker's exposure history should be sought. Occasionally these documents have proprietary agents that are not specifically listed which may cause OA, and therefore, it may be necessary for the clinician to contact the company to obtain additional exposure information.

Differential Diagnosis

A diagnosis of OA can be incorrectly made in individuals with preexisting asthma or allergic asthma due to non-workplace allergens. However, workers with preexisting asthma can still have work-exacerbated asthma. In these cases, symptoms are aggravated by exposure to irritants, physical factors (e.g., cold air), or common indoor allergens (e.g., dust mites) in the workplace. It is important to differentiate OA from other diseases such as chronic obstructive lung disease, pneumoconiosis, bronchiolitis obliterans, and endotoxin-induced asthma-like syndromes such as grain fever or byssinosis using appropriate

diagnostic testing. Whereas many of these disorders are associated with abnormal chest x-rays and diffusing capacity (DLCO), these tests are usually normal in workers with OA.

Immunologic Assessment

Immunologic mechanisms have been confirmed for many causes of OA. Therefore, it is important to investigate whether specific immune responses to suspected agents with allergenic potential are involved. Although identification of an immunologic response to a specific agent helps to phenotype different forms of OA, it is usually not diagnostic. Such a response may only reflect exposure and/or the immunogenic nature of the inciting agent. Cutaneous sensitization to an offending agent indicates a high risk for OA but lacks the specificity needed to diagnose OA. Several types of immune responses have been associated with high molecular weight (HMW) and low molecular weight (LMW) agents that cause OA. Type I, IgE-mediated immune responses have been identified for the majority of HMW proteins derived from a variety of plant and animal sources known to cause OA. IgE-mediated immune responses have also been identified as the underlying mechanism for several LMW chemical agents such as acid anhydrides and platinum salts. Although type II cytotoxic, type III immune-complex, and type IV cell-mediated immune responses have been linked to certain causes of OA, measures of specific IgE are usually the simplest and most readily available tests for diagnosing OA.

High molecular weight antigens are considered complete allergens since they do not require structural modification to elicit a specific immune response. In vivo skin testing and in vitro immunoassays have been used to identify sensitized individuals to these specific allergens. High molecular weight allergens include proteins from animal dander, insect scales, food products, and enzymes used in the food manufacturing and pharmaceutical industries. Low molecular chemical agents require structural modification to act as complete antigens. Traditionally, these reactive chemicals are coupled to a carrier molecule such as an autologous human protein (e.g., human serum albumin or HSA). The chemical hapten-protein conjugate forms new antigenic determinants, which are capable of inducing an IgE-mediated response.

It is important that the test reagents used in the diagnosis of OA be characterized and standardized. Standardization of an allergen extract requires identification of the allergen source, the extraction procedure, and its biochemical composition. The allergen source should be fresh and free of contaminants. The extraction process should record characteristics such as temperature, the medium used for extraction, the extraction time period, and the filtration methods utilized. Proper characterization should include total protein content, molecular weight range of proteins, isoelectric points of each protein, and identification of immunologic and allergenic components. The latter can be determined by a variety of techniques such as ELISA inhibition assays, Western blotting, leukocyte histamine release assays, and endpoint skin test titration techniques.

Low molecular weight chemicals can be conjugated to a carrier protein and used as an antigen for use in immunodiagnostic tests. Platinum chloride salts and sulfonechloramide represent two examples where LMW agents have been directly used as skin test reagents without prior conjugation to proteins. The most common protein carrier used is human serum albumin (HSA). Successful hapten-protein conjugation depends on the buffers used, the amount of protein and chemicals used, and the duration and temperature of the reaction. To determine the degree of chemical linkage to protein, the ratio of chemical ligand to protein carrier (mols/mole) must be established. This analysis is essential since antigenicity and allergenicity of the final conjugate may vary with ligand density. The method of analysis depends on the chemical structure of the compound. For example, spectrophotometric analysis is used to assess aromatic compounds, and free amino analysis is used for chemicals that bind to carrier amines. Gas chromatography and mass spectroscopy are the preferred methods for the analysis of aliphatic chemical-protein antigens. The ideal range of ligand binding should fall between 10 and 20 molecules of chemical per molecule of protein. Over- or under-conjugation of ligand to protein binding can result in poor test antigens. The methods described for biochemical composition of HMW complete proteins can also be used for the analysis of hapten-protein conjugates.

Clinical immunologic assessment of workers suspected for OA should include in vivo and in vitro tests when they are available. The prick skin test is the most commonly used in vivo test to assess IgE-mediated hypersensitivity responses to occupational protein allergens. The prick test concentration usually ranges between 0.1 and 10 mg/ml.

In vitro tests can detect specific IgG and IgE antibody responses to a suspected causative occupational agent. For the ELISA, allergen is bound to a plastic well with high binding avidity and then incubated with the subject's serum and antihuman IgE conjugated to alkaline phosphatase. This results in a colorimetric change, which is measured by spectrophotometry. The optical density is proportional to the amount of specific IgE in the subject's serum.

For natural protein allergens such as enzymes, ELISA-specific IgE assays are specific assays but tend to be less sensitive than skin prick testing. False-positive reactions can occur in the presence of high serum total IgE levels due to nonspecific binding, and false negatives can occur as the result of binding of a specific isotypic antibody other than IgE.

ELISA assays are also used to measure specific IgG antibodies. The significance of elevated specific IgG antibodies to a workplace allergen is less clear. There is some evidence to suggest it could represent a biological marker of exposure to chemicals such as MDI. Specific IgG antibodies to TMA-HSA conjugated antigens have been found in both trimellitic anhydride-exposed workers with hemolytic anemia and pulmonary hemorrhage and in workers with late systemic symptoms, suggesting that such antibodies may have a mechanistic role in cytotoxic or immune complex-mediated responses.

The proper interpretation of an immunologic test used in the diagnosis of OA requires validation against an accepted benchmark, such as the specific bronchoprovocation test (SBPT). Furthermore, proper standardization of an immunoassay always requires the use of well-established positive and negative control sera.

Other in vitro assays such as MCP-1, lymphocyte proliferation, and leukocyte histamine release have been used primarily as research tools in the investigation of workers with OA. Table 17.2 lists several high and low molecular weight agents known to induce OA in workers and the reported immunologic tests, which have been performed as part of their assessment. It should be emphasized that skin test responses and in vitro specific antibody responses may decline within months or years after removal from exposure from the causative agent which may limit their clinical utility in the evaluation of workers remotely exposed to a specific agent.

Physiologic Assessment

Many approaches have been used in measuring lung function in workers suspected of OA. Ideally, lung function should be monitored in the workplace during a known exposure to a suspected causative agent. However, this may present logistical problems when conditions in the workplace are not suitable for pulmonary function testing. Often, personnel experienced in proper performance of pulmonary function testing are not readily available to conduct serial testing of lung function or employers are not cooperative with such testing.

Spirometry should include the forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and the maximum midexpiratory flow rate ($FEF_{25–75}$). Assessment of cross-shift lung function (i.e., pre- and post- shift FEV1) has been used to correlate asthma symptoms to workplace exposure, but this approach lacks sensitivity for confirming OA. Multiple assessments of PEFR at work (four to five times/day) often capture enough data to diagnose or exclude OA. Furthermore, cross-shift changes in a worker's lung function have been found to be directly proportional to their level of exposure to the sensitizing agent.

Serial measurements of peak expiratory flow rates (PEFR) performed properly correlate moderately well with results of specific bronchoprovocation testing used in the diagnosis of OA. Serial PEFR measurements should be interpreted with caution due to patient noncompliance or the potential for falsification of measurements. Computerized peak flow meters which record effort and time of each measurement can improve the reproducibility and potential for unreliable readings.

Nonspecific bronchial hyperresponsiveness (NSBH) testing with methacholine or histamine is essential for confirming the presence or absence of airway hyperresponsiveness, a central feature of asthma. Subjects with a positive methacholine test and evidence of specific IgE to an HMW have been demonstrated to more likely exhibit a positive SBPT to that agent. Negative tests of NSBH are most useful in excluding a current diagnosis of OA in a currently symptomatic exposed worker.

The SBPT is considered the gold standard for the diagnosis of OA. This test should only be administered in specially equipped centers under the supervision of physicians experienced in conducting this procedure. Specific provocation testing is very time consuming and expensive to perform and therefore not readily available. However, if performed properly, the SBPT can be performed with minimal risk.

Several airway response patterns may be elicited that are characteristics for workers presenting with OA. An isolated early asthmatic response (EAR) is characterized by the immediate onset of asthma symptoms after exposure to an agent that is more commonly associated with IgE-mediated OA. An isolated late asthmatic response (LAR), which occurs until 4–12 h after exposure to the challenge agent, is more characteristic of non-immunologic OA induced by LMW chemical agents. Finally, workers with OA may exhibit a dual asthmatic response (DAR) characterized by an EAR followed by recovery period and then a LAR. Multiple physiologic patterns have been observed in OA caused by chemicals. For example, workers with diisocyanate-induced OA present 30–50 % of the time with DARs, 40 % of the time with an isolated LAR, and less than 10 % of the time with an isolated EAR.

Asthma occurring in the workplace in the absence of a latency period is characteristic of reactive airways dysfunction syndrome (RADS), also referred to as irritant-induced OA. Reactive airways dysfunction syndrome typically occurs after one or more repetitive large inhalational exposure to a toxic chemical agent such as ammonia gas, acidic fumes, smoke, or spray paints. Reactive airways dysfunction syndrome must be differentiated from the irritant symptoms which occur in patients with preexisting asthma. Irritant symptoms disappear promptly after cessation of exposure and are not associated with prolonged bronchoconstriction or bronchial hyperresponsiveness, characteristic of RADS. Workers with RADS typically do not manifest airway response patterns seen with OA induced by HMW and LMW agents. Being familiar with the different airway responses associated with various agents known to cause OA can greatly facilitate the correct diagnosis of OA.

Clinical Assessment

The first step for assessing a suspected case of OA is to obtain a careful physician-administered history. As mentioned, an occupational questionnaire is useful in capturing the necessary clinical and exposure information and to help validate information obtained by the physician-administered history. Workers with OA may present with dyspnea, chest tightness, wheezing, and cough in or out of the workplace. Upper airway symptoms such as rhinorrhea, nasal congestion, or ocular pruritus preceding the onset of asthmatic symptoms are especially characteristic of IgE-mediated sensitization to HMW agents. Symptoms may begin after immediately starting a work-shift (within 1–2 h) or several hours after starting work. Review of Material Safety Data Sheet (MSDS) is often very helpful for identifying agents known to cause OA.

If the history is positive for OA, a test of NSBH (i.e., methacholine or histamine provocation) should be performed at work or within 2 h after the work-shift. Results of this test are usually reported as PC_{20} measurements (provocative concentration of methacholine or histamine causing a 20 % decrease in FEV1). A negative methacholine test (PC_{20} >10 mg/ml) would exclude airway hyperresponsiveness (AHR) and is a good negative predictor for asthma. A positive methacholine test indicates

the presence of AHR suggestive of asthma but is nonspecific and does not confirm a diagnosis of OA. In this case, assessment of lung function performed at and away from the workplace to demonstrate airway hyperresponsiveness around the suspected agent is very useful for supporting a diagnosis of OA. When possible, a workplace challenge, which consists of supervised measurements of lung function (i.e., FEV1) in the actual work site before and during work-shifts for at least 1 week of work exposure, should be conducted. Improvement of symptoms and lung function after removal from the workplace with subsequent deterioration after reintroduction into the workplace further supports a diagnosis of OA, except in the case of RADS.

If a workplace challenge cannot be performed, peak expiratory flow rate monitoring should be conducted over 2–3 weeks at work. The worker should measure and record his/her PEFR every 3 h while awake or at least four times a day. Work exposure, symptoms, and medication usage should be recorded in a diary during this time. Diurnal variability of greater than 20 % at work as compared to normal variability at home is consistent with OA. Visual analysis of weekly plots of PEFR measurements by a blinded physician is the most reliable method of analysis. A consistent pattern of declining PEFRs at work and improvement away from work is strong evidence supporting a diagnosis of OA. Peak expiratory flow rate measurements should be interpreted with caution as workers who are seeking compensation could potentially falsify their readings.

The gold standard for the diagnosis of OA is the SBPT. If a specific substance in the workplace is suspected of causing OA and the workplace challenge is equivocal, an SBPT may be necessary. The PC_{20} ascertained by methacholine or histamine testing may be helpful for estimating the initial dose of an occupational agent prior to the specific inhalation challenge test. Because these tests are very time consuming and potentially risky, they should be performed only by experienced individuals. An SBPT should not be performed in workers with severe cardiac or pulmonary disease (FEV1 <60 %). Specific inhalation challenge tests have also been used to document causation of OA by new substances in index cases and for medical/legal purposes in proving or excluding a worker's eligibility for workmen's compensation. Although specific challenge tests confirm a diagnosis of OA if positive, negative tests do not always exclude the diagnosis in workers who have been removed from the workplace for a period of time during which bronchial AHR to the suspected agent may have resolved. It is therefore important to perform an SBPT either before or shortly after removing the workers from their workplace exposure. Another potential problem with specific inhalation challenge testing is poor standardization of methods used between different centers. Furthermore, it may not be possible to reproduce workplace exposure conditions in the laboratory since a number of technical factors such as temperature, atmospheric pressure, and concentration must be controlled in order to assure consistent exposures to chemical agents (i.e., toluene diisocyanate). In Canada, regional centers have adapted standardized methodologies for performing inhalational challenges that obviate this problem.

In addition to lung function assessment, it is important to identify whether the worker is atopic by skin testing with common aeroallergens and other appropriate allergens, especially when HMW substances are suspected of causing OA. These workers can often be skin tested using the actual agent they are exposed to such as flour, coffee beans, castor beans, and egg enzymes (Table 17.3). In vitro assays to measure specific IgE to these proteins can also be performed but are less specific than in vivo skin testing. As previously mentioned, the presence of either a positive prick skin test or serum-specific IgE only indicates IgE-mediated sensitization has occurred and does not prove a clinical diagnosis of OA.

Immunologic testing by ELISA using serum from workers exposed to LMW reactive chemicals is also useful for supporting IgE-mediated sensitization when present. IgG antibodies may represent markers of exposure to a particular chemical antigen. In vivo skin testing to LMW chemical agents has been less reliable for confirming IgE-mediated sensitization. Other in vitro techniques, such a leukocyte histamine release, leukocyte inhibitory factor, and MCP-1, have thus far been reserved for research purposes only.

Treatment

Once the diagnosis of OA has been confirmed, the treatment of choice should be to remove the worker from further exposure. Studies evaluating the clinical course of workers after removal from the workplace have found that persistence of their asthma correlated with the duration of exposure and symptoms prior to diagnosis. Individuals with OA caused by diisocyanates or western red cedar wood dust had a better prognosis if they were diagnosed early and had relatively well-preserved lung function and a less AHR. In contrast, symptomatic workers who remained in the workplace for longer periods of time experienced greater deterioration of their lung function leading to chronic persistent asthma requiring increased medication use even after being removed from further exposure. Use of respirators in the work environment generally does not reduce exposure or prevent clinical deterioration. Some studies have suggested that certain types of respirators such as airstream helmets may offer adequate protection for the worker from the offending agent; however, they are generally not considered to be adequate substitutes for absolute avoidance measures. Pharmacologic treatment of acute or chronic OA is similar to non-occupational asthma, which involves inhaled corticosteroids with or without selective long-acting β_2-agonists, leukotriene-modifying agents, theophylline, cromolyn, or nedocromil sodium; however, the latter two medications are not readily available as metered dose inhalers or dry powder inhalers in the United States. Medications can be used in various combinations depending on the severity of the worker's symptoms. Immunotherapy may play a role in the treatment of some forms of OA caused by HMW protein allergens such as laboratory animal proteins.

Prevention and Immunosurveillance

The primary categories of prevention include reducing exposure to known occupational inciting agents, identifying susceptible workers and removing them from exposure, administering workplace controls to reduce the number of workers exposed or the duration of their exposure, providing personal protective equipment in the workplace, and educating "at-risk" atopic individuals about avoidance of occupations where the likelihood for developing OA would be increased (i.e., laboratory handlers). Effective prevention of OA requires the cooperation between management and workers in the implementation of good industrial measures aimed at preventing exposure to agents known to cause OA. Every attempt should be made to minimize a worker's exposure to potentially problematic agent(s) through the institution of strict handling procedures. Workers should be continually educated about the importance of adhering to those procedures in order to avoid inadvertent exposures such as chemical spills. Prescreening of already hired workers for atopy should be considered before assigning employees to jobs where they would have inhalational exposure to sensitizing proteins (e.g., latex, laboratory animal, and enzyme proteins). Comprehensive immunosurveillance programs for detecting and monitoring workers at increased risk for exposure to known inducers of OA need to be implemented in industries that commonly use agents known to cause OA. Industries that have implemented such comprehensive immunosurveillance programs have been successful in reducing the incidence of asthma in the workplace.

Evidence-Based Medicine

1. Bernstein IL, Bernstein DI, Chan Yeung M, Malo J-L. Definition and classification of asthma in the workplace. In: Malo JL, Chan-Yeung M, Bernstein DI, editors. *Asthma in the workplace*. 4th ed. Taylor and Francis; 2013. p. 1–8.

   Asthma in the Workplace is a comprehensive authoritative book on all aspects of occupational asthma. This book is an excellent resource for any individual who is interested in learning more about occupational lung diseases. Asthma in the Workplace goes into detail regarding pathophysiology, genetics, epidemiology, disease mechanisms, specific causes of occupational asthma, clinical diagnosis, treatment, prevention, and surveillance. It is considered the most up-to-date resource on this topic.
2. Bernstein JA. Material safety data sheets: are they reliable in identifying human hazards? *J Allergy Clin Immunol*. 2002;110:35–8.

   Material Safety Data Sheets are an integral part of evaluating workers suspected of having occupational asthma. Unfortunately, these documents frequently have limitations that may thwart the clinician's ability to make a correct diagnosis of this disease. Health care individuals should understand how to interpret information provided by MSDS and recognize that they often contain incomplete information.

3. Tan J, Bernstein JA. Occupational asthma: an overview. *Curr Allergy Asthma Rep*. 2014 May;14(5):431.

This is a very comprehensive updated review of occupational asthma.

4. Quirce S, Bernstein JA. Old and new causes of occupational asthma. *Immunol Allergy Clin N Am*. 2011 Nov;31(4):677–98.

This is an updated summary of old and new causes of occupational asthma. It is a useful resource for anyone interested in OA as it discusses the causative agents and workplace exposures.

5. Bernstein JA, Ghosh D, Sublett WJ, Wells H, Levin L. Is trimellitic anhydride skin testing a sufficient screening tool for selectively identifying TMA-exposed workers with TMA-specific serum IgE antibodies? *J Occup Environ Med*. 2011 Oct;53(10):1122–7.

This study sought to evaluate the utility of screening TMA skin testing as part of an ongoing immunosurveillance program to screen workers for IgE-mediated sensitization. The results indicated that TMA skin testing correlates very well with serologic TMA-specific IgE, but when both tests are used together, the sensitivity and specificity of these screening tests are increased.

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This study found subjects with diisocyanate asthma had elevated levels of IFN-γ promoter methylation compared to workers without diisocyanate asthma. However, the role of increased methylation in diisocyanate asthma remains unclear at this time.

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This GWAS study identified several gene variants associated with diisocyanate OA, but the clinical relevance of these genes remains unclear and is the subject of future investigations.

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