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Occupational Asthma

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Abstract Occupational asthma is the most common occupational lung disease. Work-aggravated asthma and occupational asthma are two forms of asthma causally related to the workplace, while reactive airways dysfunction syndrome is a separate entity and a subtype of occupational asthma. The diagnosis of occupational asthma is most often made on clinical grounds. The gold standard test, specific inhalation challenge, is rarely used. Low molecular weight isocyanates are the most common compounds that cause occupational asthma. Workers with occupational asthma secondary to low molecular weight agents may not have elevated specific IgE levels. The mechanisms of occupational asthma associated with these compounds are partially described. Not all patients with occupational asthma will improve after removal from the workplace.

Keywords Occupational asthma · Reactive airway dysfunction syndrome (RADS)

Epidemiology of Occupational Asthma

There are 25 million asthmatics in the USA, but estimates of the fraction that have occupational asthma (OA) vary widely. The reported prevalence of OA among all adult asthmatics ranges between 2% and 36% [1, 2]. It is estimated that up to 25% of all "adult-onset" asthmatics have a workplace trigger for their disease. One explanation for the varied prevalence rates is that the OA diagnosis may not be as stringent in some retrospective studies as it is in documented worker compensation cases. In one of the largest retrospective series covering three decades of studies, Blanc and Toren concluded that one in ten adult asthmatics had an occupational trigger for their disease [3]. The more conservative estimate, therefore, is that the prevalence of OA is 5–10% of all adult asthma cases.

Despite more streamlined improved reporting systems, the true incidence of OA remains unknown. Twenty-five new cases of OA per million population were reported annually in the UK in the 1990s, while 3–18 cases per million were reported in the USA [4–6]. Several large organizations track incident cases, including the Surveillance of Work-Related and Occupational Respiratory Diseases [7] in the UK and Sentinel Event Notification System for Occupational Risks (SENSOR) [5] in the USA. The SENSOR program documents occupational diseases in four states (California, Michigan, Massachusetts, and New Jersey) and is a rich source of epidemiologic data.

The economic impact and morbidity of OA is substantial when costs from lost work productivity, disease treatment, employer and employee health insurance costs, and legal fees are considered. Five percent to 20% of all asthmatics suffer partial disability that affects their ability to work [8], and 40% to 80% lose considerable income as a consequence of their disease [9, 10]. Using a proportional attributable risk of 15% for both asthma and COPD, Leigh and colleagues estimated the 1996 US costs of OA at US $1.6 billion and the COPD costs at US$5 billion [11]. Clearly, both OA and COPD are diseases that place considerable financial burdens on patients, employers, and public health systems. Prevention strategies likely will be the only cost-effective intervention to tackle this problem.

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Updated Definitions for Work-Related Asthma

In 2008, the ACCP published their updated state-of-the-art consensus statement on the "Diagnosis and Management of Work-Related Asthma" [12]. This is one of the several major government or professional society guidelines that have been rewritten and published in the past 3 years. The National Institute of Occupational Science and Health (NIOSH) rewrote their "State-Based Surveillance" consensus definitions for occupational asthma, which are available online through their www.cdc.gov/niosh website. Similarly, the British Thoracic Society and the Agency of Healthcare Research and Quality consensus statements are publicly available [13, 14]. These collective efforts, particularly those of the ACCP, have significantly improved the standardization of the terminology and definitions for asthma in the workplace, which previously varied considerably [5, 7, 15].

The term occupational asthma does not correctly refer to all patients suffering from asthma in the workplace (Fig. 1). The term occupational asthma encompasses all workers who develop new respiratory symptoms and obstructive airways physiology consistent with the diagnosis of asthma, and the cause can be directly attributed to an exposure in the workplace. The key element is that OA is asthma caused by an organic protein, chemical, or other compound unique to the workplace. OA is further split into two subtypes—sensitizer-induced OA (>90% of the cases) and irritant-induced asthma including reactive airway dysfunction syndrome. Work-exacerbated, or work-aggravated, asthma refers to previously diagnosed asthma that is worsened, but not caused, by agents found in the workplace. The distinction between these two entities is not superfluous as it impacts treatment strategies and medico-legal decisions. Millions of people with established asthma work and exacerbations of disease can occur in the workplace. Clearly, these patients should not have their work eligibility affected by their disease, and in general, their symptoms should be controllable. Patients with preexisting asthma whose disease becomes uncontrolled in a new work environment should be evaluated as a new case of OA. OA, therefore, represents the majority of asthma cases caused by an agent in the workplace, and the evaluation and diagnosis of this entity must follow established protocols and guidelines.

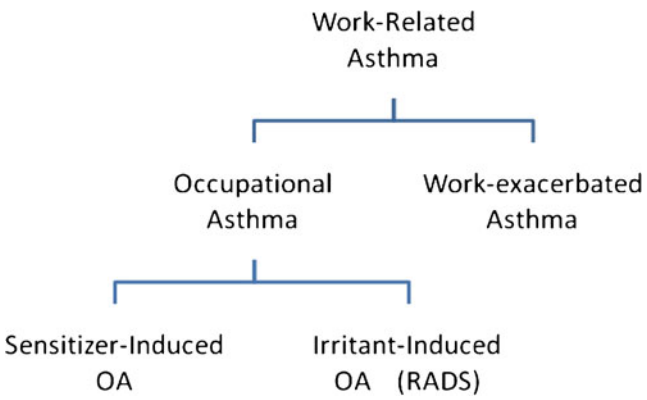

Fig. 1 Classification scheme for the major types of asthma in the workplace. This scheme is based on the American College of Chest Physicians 2008 guidelines and is adapted from Tarlo et al. [12]

Reactive Airways Dysfunction Syndrome: "Classic" Irritant-Induced Asthma

Reactive airway dysfunction syndrome (RADS) refers to an asthma-like respiratory syndrome due to irritating vapors, fumes, or smoke in individuals with no prior respiratory disease. The incidence of RADS as a portion of new-onset OA ranges as high as 25% [16] with 9.3–10% [17] as a more typically reported range. Scenarios which lead to RADS often involve inadvertent exposure to multiple workers. It is likely that any mucosal irritant may lead to RADS if administered at a high enough exposure level. Some of the identified agents are listed in Table 1.

The initial respiratory symptoms of RADS may manifest within minutes to hours of exposure to the implicated irritant. Previous exposure or previous sensitization is neither required nor characteristic of this syndrome. Rather, a rapid time course to symptoms, no prior exposure history, and good prior respiratory health are characteristic of the syndrome. The non-immunologic, lymphocyte-predominant response that is characteristic of this syndrome is attributed to direct airway injury caused by the inhaled irritant. While most individuals with RADS will have a single identifiable exposure, some may have multiple exposures to the irritant. Most criteria for RADS also require the symptoms to be present 1 month after exposure to distinguish RADS from the direct toxin-mediated pathology. Persistent respiratory symptoms are typically managed with bronchodilators and assiduous irritant avoidance. The course of disease may resolve over weeks to years or, in some case, persist indefinitely.

Table 1 Selected reports of RADS and causative agents

Agent	Setting
Glacial acetic acid	Hospital chemical spill
Phtalic anhydride	Truck tanker spill
Hydrogen sulfide	Swine confinement facility
Various	World Trade Center site
Methyl isocyanate	Bhopal chemical plant
Denitrogen tetroxide	Railroad tanker spill
Hydrofluoric acid	Household exposure

Noteworthy exposures include the Bhopal chemical plant toxic gas release in India and the World Trade Center (WTC) collapse in New York [18, 19]. In Bhopal, India, 30 t of methyl isocyanate was accidentally released overnight on December 3, 1984. Some 2,500 people died acutely and many more incurred less than lethal injuries. Retrospective evaluations found persistent respiratory complaints and RADS-like pattern in exposed individuals [20] In New York, rescue personnel were exposed to various inhaled irritants during the rescue efforts after the destruction of the WTC. Quite early, Prezant and colleagues [19] recognized WTC cough and RADS among the exposed individuals. Dust samples collected within the first 48 h included high levels of glass fibers, cement, silicates, asbestos, and polycyclic aromatic hydrocarbons [21]. High percentages of particulate matter ≤2.5 μm were found in suspended dust 1 month (16–86% of total dust) and 6 months (7–85%) after the WTC attack [22]. The incidence of irritant-induced occupational asthma among first-responder personnel was reported to be quite high initially. Longer-term studies in well-characterized subjects suggest that the incidence of irritant-induced OA in WTC rescue personnel is 22.6% [23].

Making a Diagnosis of Occupational Asthma

Making an accurate diagnosis of OA requires that several key relationships between asthma and work be established. In essence, the following three criteria need to be met:

- A worker receives a diagnosis of de novo asthma or recrudescence of previously quiescent asthma.
- A worker is exposed to a sensitizing agent or an irritant in the workplace that is known to cause OA.
- A sufficient causal relationship is established between the causative agent and the worker's symptoms.

In addition to the clinical history and physical examination, several other tools should be employed to investigate the potential causal relationship between asthma and the workplace. These include symptom diaries, employment questionnaires, lung function testing with consideration of methacholine challenge testing, peak flow rate monitoring performed at and away from work, immunologic testing, and occasional workplace site visits.

The Adult Asthmatic with Occupational Asthma: Clinical Presentation

Episodic wheezing, dyspnea, cough, and nocturnal awakenings are the typical presenting complaints of an adult patient with OA. These symptoms do not differ from that of other asthmatics, but the care provider should consider the diagnosis of OA in the newly asthmatic adult patient. Shortness of breath with or without wheezing was the chief complaint of 36% of workers exposed to wood products containing methylene diphenyl diisocyanate for up to 8 months, with a slightly increased figure of 45% at 20 months. The second most common symptom in this cohort, chest tightness, occurred in 38% of these workers at 20 months. These symptoms plus cough, phlegm production, and sudden attacks of shortness of breath occurred in at least 25% of all workers by 20 months. While the chief complaints in OA may not differ from those with other forms of asthma, the temporal nature may vary. Patients with OA may report that their symptoms are better on the weekends and worse at the end of the workday or at night. Asking directed questions regarding the timing of the symptoms is the key to eliciting an OA clinical history. Several questions include:

- Were there changes at the workplace in the period preceding symptoms?
- Was there a notable exposure at work in the day prior to the onset of symptoms?
- Are there other associated symptoms such as runny nose or itchy eyes?
- Is there a noticeable difference in symptoms at home during the weekend, or on vacation?

This last question has a very high sensitivity (88–90%) for the diagnosis of sensitizer induced OA, but it is not specific. At best, clinical history and examination can provide a correct diagnosis of OA in 75% of cases, but these estimates come from studies of patients with high pretest probabilities of OA referred for specific inhalation challenge [24]. Realistically, the likelihood of making a correct diagnosis of OA based on history and physical alone is probably about 50%. Further testing and more thorough evaluation is frequently warranted.

Worksite Evaluation

Questionnaires can help determine the extent of a worker's exposure to specific compounds, but a workplace visit and an on-site investigation may be necessary in some instances. The focus of these assessments is two-fold. First, is the asthmatic exposed to a single agent in the workplace that is known to cause asthma? Second, is there a clear temporal association between the patient's symptoms and the workplace exposure to this agent? Questions should address the time of day that symptoms develop and whether these symptoms resolve during extended breaks from work (e.g., weekends or vacations). One study reported that only 50% of pulmonologists and allergists asked about the

association between asthma symptoms and work habits [25]. A failure to ask such questions may lead to the wrong diagnosis.

More than two hundred fifty specific agents have been causally linked to OA, but most cases of OA are caused by only a handful of compounds. Table 2 lists some major classes of compounds that are known to cause OA and the industries that often employ them. Clinicians must elicit a detailed work history in adult onset asthmatics. Specific job duties, date of hire, and job environment should be asked directly and documented in an evaluation. Often, workers are unaware of all the products used in their industrial plant, and clinicians should ask that the worker or the worker's employers provide copies of the material safety data sheets (MSDS) from their employers and any reports from worksite visits. Occupational Safety and Health Administration (OSHA) requires that potential sensitizing agents that are >1% of the chemicals in compound are product be listed in the MSDS. While all physicians have the right to request and review the MSDS from employers, this is a time-consuming process and is unfortunately often forgotten.

Inhalation is the primary portal of entry for chemicals and other compounds and repeated exposure leads to systemic sensitization. An evaluation of the exposure risk for a worker often cannot be done efficiently without help from outside experts. Occupational hygienists or occupational medicine professionals specialize in sampling techniques and sensitive assays, such as liquid chromatography, gas chromatography, and mass spectrometry, to measure concentrations of particulate airborne compounds. Unless trained in this highly specialized area, clinicians should focus their efforts on the patient's complaints as they pertain to the worksite.

Lung Function Testing

Once clinicians suspect a temporal relationship between a patient's asthma symptoms and the workplace, they should order complete lung function testing, including spirometry with and without bronchodilator, lung volumes, and diffusion capacity testing. Measurements of peak expiratory flow rates (PEFR), usually with an inexpensive handheld device, must be performed at the worksite and away from it. Newer patient-activated, portable devices store full spirometry data including FEV_1 readings, but they remain expensive. These devices record and log spirometry readings and reduce the problem of falsified records. Training in the forced vital capacity maneuver and adherence to PEFR and spirometry measurement diaries is essential.

One formal study of serial PEFR during and after work is named the "stop-resume work test" [26]. Essentially, this test asks that the worker monitor and record at least four serial peak expiratory flow readings a day while at work and at home. This test is repeated for several continuous weeks, including weekends and rest days. The OASYS scoring system (Fig. 2) has sensitivity of 78% and specificity of 92% for the diagnosis of OA when serial PEFRs are recorded at least four times daily for greater than 3 weeks, and a sensitivity of 64% and specificity of 83% when PEFRs are recorded less than four times a day for less than 3 weeks [27]. Workers with asthma caused by an occupational agent will demonstrate significant peak flow variability (20–30%) with higher readings on weekends and lower readings during and after work. Such a variation should not be seen with asthmatics who do not have a workplace trigger. It is important that clinicians ask that measurements be recorded over days to weeks, but adherence to this regimen can be difficult.

In addition to spirometry, repeated airway hyper-responsiveness measurements with methacholine challenge testing (MCT) provide strong evidence for OA. MCT will change depending on whether the OA patient has been recently exposed to the agent that caused their OA or whether they have been away from work for an extended period (>2 weeks). A three-fold difference in the methacholine concentration required to trigger a positive response (a 20% decrease in the forced expiratory volume in one second FEV_1) is strongly indicative of OA. There are a few studies supporting repeated MCT to diagnose OA, but it remains a valuable tool for occupational medicine specialists and its use is supported in consensus guidelines.

An OA diagnosis can be wrong even when it is based upon accurate symptom data, spirometry readings, and MCT results. Several studies published in the mid-1980s to early 1990s showed a discrepancy between the clinical diagnosis of OA and the diagnosis confirmed by specific inhalation challenge, the gold standard test [28, 29]. In one study, 63 workers diagnosed with OA by specialist physicians secondary to isocyanate exposure underwent inhalation challenge testing to isocyanate [29]. Only 48% of the workers demonstrated airway hyper-responsiveness to isocyanates, although most workers reported respiratory symptoms during the test. Forty-three percent of the

Table 2 Common low and high molecular weight compounds that cause sensitizer-induced OA

Low molecular weight compounds	Occupations
Isocyanates	Plastics workers, painters, insulators
Anhydrides	Plastics and resins workers
Amines	Lacquer and shellac workers
Metals (e.g., platinum, vanadium salts)	Platers, welders, chemical workers
Chloramine-T	Cleaners

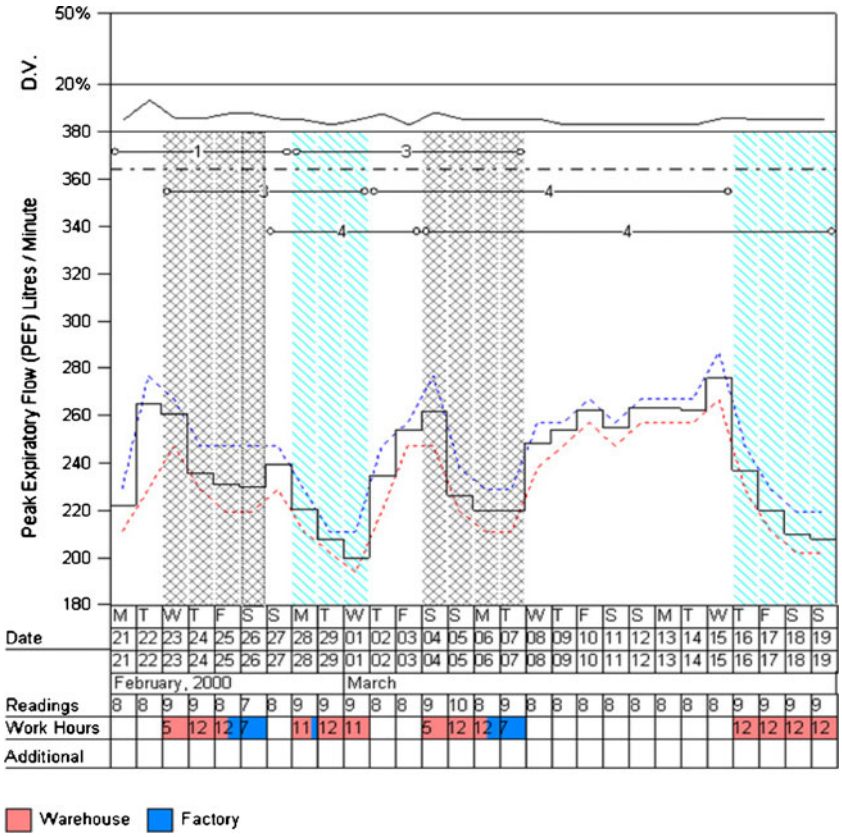

Fig. 2 Occupation Asthma System (OASYS) plot of serial peak flow rates (PEFR) at work and at home. This is a well-validated computer-aided tool to assist in the diagnosis of occupational asthma based on patterns of PEFR change

workers had no response to isocyanate but showed airway hyper-responsiveness to methacholine. Proving a causal relationship between a specific compound and a worker's asthma is not straightforward.

The Old Gold Standard: Specific Inhalation Challenge

Specific inhalation challenge (SIC) mirrors other inhalation challenge testing except that patients are exposed to aerosols of occupational antigens. While considered the "gold standard" test to document OA, SIC is not performed commonly in the USA and cannot be considered part of the standard evaluation. In many countries, clinicians order SIC routinely. A recent survey of 123 US and Canadian pulmonary and allergy medicine training programs found that only 15 centers performed SIC tests [30]. Of 2,065 patients diagnosed in the USA with OA in the preceding years, only 130 (6%) had been diagnosed with the help of SIC testing. In contrast, 130 of 308 of OA cases (42%) in Canada underwent SIC testing. Sixty percent (74 of 123) of the training programs believed SIC was useful, but only 55% of the respondents could order the test if they wanted it. A list of the 15 centers performing SIC in the USA and Canada can be found in the 2002 manuscript of Ortega and colleagues [30].

As with most "gold standards," problems exist with SIC. False negative tests with SIC occur if the wrong compound (e.g., wrong isocyanate) is chosen or if SIC is performed long after the worker has left the workplace. Sastre and colleagues demonstrated that five of 22 workers with apparent isocyanate-induced OA had a negative SIC, but three of these five workers were subsequently positive when tested a second time [31]. Despite these deficiencies, SIC remains the gold standard test for making the diagnosis of OA in as many as 50% of patients in Canada and throughout much of the world. The same cannot be said for the USA where SIC is rarely ordered and performed.

Immunologic Testing

Skin prick testing and in vitro IgE-specific assays can determine if a worker has developed an antibody response to a high molecular weight (HMW) protein or glycoprotein in the workplace. They are not particularly useful in investigating low molecular weight (LMW) sensitizers since IgE responses to these compounds are inconsistent. A positive skin prick testing test to an agent known to cause OA is helpful in identifying the nature of the exposure, while a negative test has a high negative predictive value for ruling out a specific exposure. Testing for an IgE-mediated response to a panel of common high molecular weight proteins is relatively straightforward, while testing for low molecular weight antigens, such as diisocyanate, is

not. Diisocyanate, for example, may lead to elevated IgE levels in only 20–30% of exposures where it appears to act as a hapten [32]. Nonspecific RAST and hypersensitivity panels may prove helpful in some patients specifically exposed to Aspergillus or other fungi at work. Newer commercially available in vitro assays are becoming available to detect isocyanate and other low molecular weight agent-induced OA. For example, the production of monocyte chemotactic protein-1 by peripheral blood mononuclear cells in patients with diisocyanate-induced OA can distinguish them from non-asthmatic workers [32]. Overall, however, experience is limited, and with these kits and larger scale reports need to be published. In our experience, skin prick tests provide important supporting data demonstrating sensitization to occupational antigens.

Other Diagnostic Studies

Surrogates of airway inflammation, like sputum eosinophilia and exhaled nitric oxide, contribute to the management of patients with asthma, and these markers are now being evaluated in OA. In a cohort of asthmatic patients without OA, Green and colleagues showed that the number of exacerbations decreased significantly when patients were managed by maintaining sputum eosinophil counts less than 3% or exhaled nitric oxide concentrations less than 5.0 ppb. This approach has been applied to OA, as well. For one, peripheral blood and airway eosinophilia is evident in all forms of OA, including RADS, and induced sputum eosinophils and neutrophils increase after exposure to specific work-related compounds, like isocyanates [33]. In one study, serial spirometry measurements plus induced sputum eosinophil counts improved the accuracy of the OA diagnosis compared to spirometry testing alone [34]. Compared to sputum eosinophil counts, however, data with exhaled nitric oxide in OA is scant. One study documented that exhaled nitric oxide levels increased in workers with a positive inhalation challenge and not in those with negative tests in a small cohort of 40 workers [35]. The potential strength of the exhaled nitric oxide test lies in its use for disease management. At this juncture, induced sputum eosinophil counts and exhaled nitric oxide measurements cannot be recommended in supporting the diagnosis of OA or in managing OA patients, and in general, diagnosis is based on clinical logic (Fig. 3).

Gene Polymorphisms and Occupational Asthma

Genetic polymorphisms are a research focus in asthma, and this has spilled over to OA as well. Obviously, a genetic profile that potentially predisposes workers to an increased

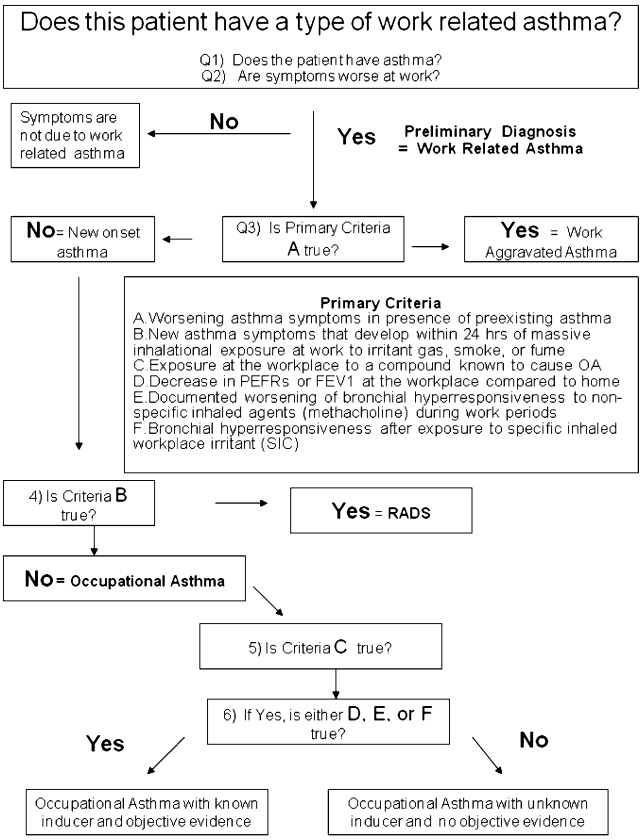

Fig. 3 Flowchart depicting stepwise approach to work-related asthma. It is adapted from the National Institute of Occupational Safety and Health (NIOSH) "Decision Logic" worksheet that is part of their NIOSH Work Related Asthma Surveillance program

incidence of OA would be on interest to certain industries with high incidences of OA (e.g., animal care and food industries). While no such gene has been identified to date, researchers continue to focus on two candidate families: the glutathione *S*-transferase (GST) and HLA family. The GST family of genes involves a host of enzymes that protect the host lung epithelium from oxidative stress. The GSTP1 Val/Val genotype has been associated with both allergic asthma and toluene diisocyanate (TDI)-induced OA [36, 37]. In one study, the presence of GSTP1 Val/Val genotype appeared to have a protective effect against OA in workers exposed to TDI over 10 years [38]. Broberg and colleagues investigated the association between genotype and toluene metabolites (i.e., toluene diamine, TDA) in workers exposed to TDI [39]. They found that workers with the GSTP1 105 Val/Val genotype had about one half of the levels of TDA in the serum and urine compared to workers with other GSTP1 105 variants, thereby suggesting that genotype affected retention and exposure to TDI. Other genes in the GST family appear to confer an increased risk of OA also.

The second class of genes of interest in OA is the HLA class II molecules—part of the major histocompatibility

complex—that are involved in antigen presentation. Young and colleagues demonstrated a strong correlation between increased expression of HLADR3 and the development of OA after exposure to trimellitic anhydride [40]. However, this correlation is not apparent with exposures to other compounds.

Pathogenesis of Occupational Asthma

As with all asthma, the mechanisms leading to the development of OA are not fully known. Two major classes of agents—HMW and LMW agents—cause OA, and the mechanisms appear to differ significantly. Common HMW organic proteins that cause OA include grains, latex, animal-derived proteins, and seafood. More than 140 LMW chemicals and compounds trigger sensitization in humans, and this list includes isocyanates (e.g., TDI), anhydrides, dyes, and smaller organic compounds.

High molecular weight antigens (>5,000 kDa in size) act like other environmental antigens that lead to sensitization and IgG and IgE antibody production. In general, months to years of exposure are necessary to develop this allergic response, and latency helps distinguish OA from RADS. HMW organic proteins can trigger a vigorous immune response, and the period of latency may be less than 1 year. A recent, prospective study following 118 apprentice bakers and new animal workers found that 64% of the new hires developed positive skin prick test responses to grains and animal proteins; yet, only 12% developed asthma symptoms [41]. The incidence of occupational rhinitis in this study was higher than OA, which is consistent with most studies.

The pathways leading to systemic sensitization to HMW proteins and polysaccharides do not differ significantly from the pathways involved in the development of environmental asthma. Briefly, a HMW antigen, such as an animal dander protein, will associate with and MHC II molecule on a dendritic cell and be transported to a lymph node. An allergenic peptide sequence will interact with naïve T cells and some undergo transformation to Th2 or Th1 cells. Cytokines (IL-4, IL-5, and IL-13) from these cells then stimulate IgE production from B cells and eosinophil recruitment from the bone marrow. The pathologic sequence in IgE-mediated OA resembles that of more common forms of asthma, except the sequence of events can occur more rapidly.

The development of OA from LMW compounds can result in a type I, IgE-mediated immune response by acting as haptens, but in most cases, it does not. Admittedly, evidence supporting the concept that LMW agents act as haptens is slim. It has been suggested that the degree of hydrophilicity of the LMW compound may impact its function and determine whether it stimulates a type I immune response. Hydrophilic LMW compounds, for example, may cross the respiratory epithelial membrane more readily, bind lung proteins, and trigger IgE production, while more hydrophobic compounds may not.

Most LMW agents, like TDI, cause a delayed type III, cell-mediated immune response by binding to organic macromolecules at the airway–epithelium interface. This inflammatory response appears to occur more rapidly than with HMW compounds [42] and is characterized, in part, by increased numbers of airway CD8+ lymphocytes. Affinity of certain LMW compounds for various organic proteins and other adducts has been shown. Trimellitic anhydride, for example, can bind with amino groups, alcohols, and epithelial cell proteins [34]. Intracellular glutathione may also act as a transfer molecule for LMW agents and serve as an intermediary in the development of the allergic response [43].

Another factor that may enhance sensitization to LMW compounds is tobacco smoke. Workers exposed to second-hand environmental tobacco smoke at work have a higher incidence of work-related asthmatic symptoms [44]. As an example, the risk of sensitization to platinum salts in refinery workers is higher in workers who smoked [45]. Overall, the diverse mechanisms involved in the development of LMW antigen-associated OA are interesting and further investigation will provide information to determine the relevance to all asthma.

Specific Cases of Interest

Based on surveys from NIOSH, the prevalence of OA in hospital and biomedical workers is as high as 15% [46]. We will discuss three types of exposures in workers in the biomedical field that commonly present to clinicians for evaluation of respiratory symptoms: (1) cleaning staff, (2) all hospital staff exposed to latex, and (3) laboratory workers who handle animals.

Cleaning Solutions and Asthma

Compounds in cleaning solutions can be both respiratory irritant and sensitizers. The incidence of OA in cleaning staff either has increased significantly or, more likely, is much better recognized. Fifteen percent of new OA cases in Catalonia, Spain in 2002 were caused by cleaning agents, while cleaners made up 12% of new WRA cases in the USA in the SENSOR surveillance program [47, 48]. One hospital studied the exposure problem among its cleaning workers and identified mirror cleaning, sink cleaning, and toilet cleaning with disinfectants (ammonia, isopropyl alcohol, 2-butoxyethanol, mono-ethanolamine) as the high-

est exposure activities [49]. The recognition of the dangers of volatile organic compound exposures in cleaners is still quite new. It is likely that new exposure standards and preventive measures will be addressed.

Latex Allergy and Asthma

Allergy and OA related to latex and natural rubber compounds represent a significant and illustrative example of occupational illness. Latex-related allergy and asthma was recognized first in the 1970s in latex-exposed patients, such as those with spina bifida. It gained prominence during the late 1980s and 1990s with the implementation of NIOSH/CDC universal precautions for blood-borne infections. The CDC precautions increased the use of latex gloves and heightened worker exposure to natural rubber products. As with other examples of HMW agent-related OA, the incidence and severity of disease correlates with exposure level. Currently latex-related OA represents some 4% of all work-related asthma cases (10.3% in Michigan). Diagnosis is similar to other OA cases with the exception of immunologic testing. RAST testing is less sensitive in the case of latex allergy and OA with nearly a 30% false negative rate as compared to patch or skin prick testing.

While latex allergy and OA are present in other industries (e.g., food handling, manufacturing), the incidence is twice as high in health care workers (5–18%) as in the general populace [50], and it is more prevalent in work areas with high level exposures to latex gloves and glove dust. With the recognition of latex allergy as a problem, NIOSH implemented recommendations to decrease the incidence of latex-related allergy and OA by decreasing workplace latex antigen exposures. In hospitals where these recommendations are implemented (the use of powderless gloves, non-latex gloves, and gloves of higher-quality manufacture techniques), the incidence of latex-related OA and allergy has decreased [7].

Occupational Asthma in Animal Workers

The incidence of atopic sensitization to small laboratory animals and pets is reported between 15% and 40% [51] and pre-existing atopy to environmental allergens is the primary risk factor for developing animal allergy. Two million people work in jobs that expose them constantly to animals. Inhalation of animal proteins in dander, fur, feces, urine, and saliva can lead to sensitization. Proteins isolated in the urine of rodents, called lipocalins, for example, trigger an IgE-mediated response. Lipocalin sequences are now added to skin prick and RAST panel tests. While low exposure to these proteins can lead to sensitization and OA, high exposure time increases these risks significantly. Implementation of prevention strategies that decrease total exposure to inhaled animal proteins remains a key goal for NIOSH and should be for all medical centers and industries.

Prevention of Asthma in the Workplace

Screening for pre-existing atopic conditions in new workers is not legal; therefore, employer interventions must be aimed at limiting exposures to certain airborne antigens. The OSHA and NIOSH regulations regarding worker contact with specific compounds often appear burdensome to industry, but these regulations will remain the primary strategy to combat OA (Table 3). These recommendations encourage employers to formulate their own policies and procedures regarding this issue. Ventilation and individual protection strategies are near the top of many NIOSH recommendations for specific worker groups. A proactive employer will institute these guidelines and a workplace screening program [52]. Small studies have shown that such measures can decrease the incidence of OA. In one recent example, Grammer and colleagues offered personal protective masks to 66 workers newly hired in a plant producing an acid anhydride [53]. Over 7 years, the workers who used the protective masks decreased their absolute risk of developing rhinitis or OA from 10% to 2%. Preventing exposure to airborne agents should decrease the incidence of OA, but installation of new ventilation systems is costly for employers, and personal protective industrial masks and helmet respirators do not seem practical to many workers.

Treatment

Minimizing allergen exposure is an essential component of every asthma treatment plan. Similarly, quitting work or avoiding the worksite exposure is the primary treatment in

Table 3 Key activities to prevent asthma in the workplace

Identify and move susceptible workers to work areas without exposure to known sensitizers.
Known asthmatic patients should have limited exposure to potential respiratory irritants
Elimination of a sensitizer agents, and substitutions with safer substances, improved facility ventilation, increased dust reduction techniques, and better housekeeping practices are all appropriate interventions to decrease the incidences of work related asthma.
Job rotation, rest periods, shift, or location changes may reduce the number of workers exposed or duration of exposure
Workers should wear personal protective equipment, which includes respirators, gloves, goggles, and coveralls, when appropriate.

Adapted from Tarlo et al. [52]

OA. Inhaled corticosteroids, long-acting β2-agonists, and rescue drug medications should be prescribed according to the guidelines of the NAEPP [54], but the efficaciousness of these therapies in OA is less well established.

Studies have shown that patients that remain in the workplace after the diagnosis of OA suffer worsening lung function despite appropriate steroid therapy [9]. In one cross-over study, Malo and colleagues found that the addition of inhaled corticosteroids worksite removal did improve asthma symptoms, airway hyper-responsiveness, and quality of life measures more than work removal alone [55]. In another recent study, Marabini and colleagues treated 20 OA patients who remained at their job with beclamethasone dipropionate (500 μg BID) and salmeterol (50 μg BID) for 3 years [56]. At the time of enrollment, their FEV_1% predicted was mildly reduced at 80.2%. After 3 years, lung function remained the same, as did airway hyper-reactivity, symptoms, and rescue β2-agonist drug usage. While lung function and symptoms did not improve with inhaled corticosteroid treatment, neither did they worsen. The authors surmised that the outcome in these 20 workers might be the same with adequate controller therapy, whether they quit or continued to work. At this time, this approach cannot be recommended. Larger, prospective studies needed to evaluate this question may never be performed.

Management of work-aggravated asthma, where asthma is a pre-existing condition and the disease flares with work exposures, differs from that of OA. Avoidance of worksite exposures is important, but pharmacotherapy can control symptoms. In general, fewer workers with work-aggravated asthma lose their jobs than workers with OA. This practice may be influenced both by the medico-legal complexities associated with OA and the belief that work-aggravated asthma represents a milder form of the disease [57]. Like work-aggravated asthma, irritant-induced asthma or RADS is amenable to drug therapy and workers often return to their jobs.

Outcomes for Workers with Asthma

Unfortunately, asthma symptoms and airway hyper-responsiveness persist in many patients after removal from the worksite and, in this sense, OA mirrors environmental asthma. More than 50% of workers with OA have persistent asthma symptoms and airway hyper-responsiveness in the years succeeding their quit date. As should be expected, specific IgE to the offending compound that caused the OA decreases significantly once the worker leaves. Immune cell memory does not fade completely, however, and re-challenge with the same compound 2 years later will trigger an asthmatic attack in the vast majority of those affected.

Biologically, it makes sense that once an insult—be it an environmental, infectious, or an occupational one—triggers structural airway changes, such as airway wall thickening and smooth muscle hypertrophy, the disease will not abate completely in all patients. Simple avoidance alleviates, but does not necessarily cure, the disease. Nonetheless, early removal from the workplace portends a better prognosis.

Compensation and Disability

The economic realities of OA for a worker can be overwhelming and life changing. Several groups have studied the economic impact of OA on workers, and an interesting review on this topic has recently been published. In one study of 55 US workers with OA, 69% remained unemployed an average of 2.5 years after the diagnosis [58]. In Vandenplas and colleagues' meta-analysis of six studies from three European countries and Canada, about one third of workers with OA reported prolonged unemployment or work disruption and one half to two thirds reported significant lost income [57].

Diagnoses of OA inherently lead to decisions regarding the impairment, disability and compensation of workers. Physicians should advocate for workers diagnosed with OA and adopt a pro-active approach by reporting the diagnosis to compensation boards, surveillance organizations (e.g., SENTINEL), government agencies (e.g., OSHA), and possibly employers. Impairment and disability programs are exceedingly complex and differ significantly among states and countries. In general, impairment is based on the degree of lung function compromise. Workers with objectively recorded and diagnosed OA should receive temporary disability immediately and decisions regarding permanent disability should be made after some period of observation and review. Most workers receive complete, permanent disability for the job that caused their OA and for any job where they might be exposed to the same product or compound. The role played by physicians should focus on making an objective and accurate diagnosis. If the diagnosis of OA is established, physicians should initiate appropriate controller drug therapy, remove patients from the work environment, request temporary disability from that job, and report the case to the appropriate monitoring and surveillance boards.

Conclusions

OA is the primary lung disease in the workplace and is of increasing importance to OSHA, state regulatory boards, and employers. Every measure must be taken to prevent sensitization to occupational antigens that commonly cause

OA and occupational rhinitis. Studies in the past decade have helped to elucidate some of the mechanisms leading to asthma secondary to HMW and some LMW compounds, but other pathways need exploring. Many workers remain symptomatic and suffer continued loss of lung function after being removed from the work environment. Disability and compensation issues will become increasingly common, and the specialist will need to remain updated on this important disease.

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