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Occupational asthma: what can be done to prevent it?

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Occupational asthma (OA) accounts for at least 10% of cases of adult asthma and presents as intermittent asthma occurring at the workplace and remitting on weekends and holidays, or persistent asthma, especially if the diagnosis and early intervention is delayed. OA is under-recognized, challenging and time-consuming to diagnose, difficult to confirm with currently available tests and complex in terms of legal implications of disability and impairment. Over 400 agents have been identified as causing OA with allergic triggers accounting for 80–90% of cases. Managing the worker with OA is demanding as it requires the most thorough evaluation with attention to detail to provide an accurate diagnosis and develop a thoughtful treatment recommendation. This frequently has to occur in the context of various competing entities including management, unions, insurance carriers and attorneys. The primary goal is excellent employee health through interventions that may allow the worker to continue in their occupation safely. Primary, secondary and tertiary prevention measures have been adopted for various types of OA with success. Novel approaches may become available and be beneficial to identify and treat OA early before severe, chronic, unremitting and irreversible changes occur.

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Occupational asthma (OA) is a major cause of pulmonary disease in adults and the most common occupational respiratory disease in industrialized countries. OA can be broadly defined as asthma caused by work exposure or more specifically defined as variable or partial airway obstruction that is usually reversible either spontaneously or with treatment, or bronchial hyper-responsiveness (BHR) resulting from the inhalation of airborne agents present at the workplace [1]. These agents can include dusts, chemicals, proteins, vapors, gases and fumes. Occupational exposures can also aggravate pre-existing asthma. Although the pharmacological treatment for OA does not currently differ from that of non-OA, the major emphasis is prevention of OA through early identification and avoidance of the agent, monitoring airborne levels and prompt treatment. A recent 'state of the art' article by Mapp and colleagues comprehensively reviews OA with emphasis on definition and causal agents, epidemiology and risk factors,

pathophysiology, natural history, long-term consequences, diagnosis, management and prevention [2].

This article briefly reviews the current state of OA with emphasis on primary, secondary and tertiary prevention strategies to curb the rise and impact of this disease that places an enormous economic and social burden on society. Although innovative strategies to prevent OA could be developed for each individual allergen in every occupation, due to the vast numbers of OA triggers identified, space constraints restrict this article to general principles using specific illustrative examples.

Pathophysiology

In broad terms, OA is inflammation of the airways caused by a nonimmunologic irritant mechanism or an immunologic mechanism that is either immunoglobulin (Ig)E-dependent or non-IgE dependent. Knowledge of the type of pathologic mechanism is fundamental to developing methods of identifying and monitoring

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sensitized workers. A nonimmunologic mechanism of bronchoconstriction caused by a neurogenic reflex after inhalation of a toxic substance cannot be confirmed using immunologic testing. This type of acute OA occurs immediately after a large inhalation exposure of a corrosive substance, such as ammonia, fire smoke, chlorine gas or hydrochloric acid, in an individual with no previous lung disease and is termed reactive airway dysfunction syndrome (RADS) [3]. An example is firefighters developing cough and BHR after excessive exposure to smoke and dust at the World Trade Centre site in 2001 [4]. In terms of recognition, RADS is relatively straightforward and prevention entails careful review and adherence to safe working and handling procedures of chemical or other agents using proper precautions including containment of the agent, personal respiratory protection, adequate ventilation and prompt clean up.

An IgE-mediated allergic mechanism requires a sensitization period before symptoms occur. These agents are typically high molecular weight (HMW) allergens and less likely low molecular weight (LMW) chemicals. Examples of HMW allergens include flour (bakers), latex (nurses and other healthcare workers), enzymes (detergent industry) and animal proteins (farmers, researchers or laboratory animal workers). Most cases begin within 1–2 years of exposure and affect a relatively small proportion of workers. Skin prick tests or *in vitro* specific IgE assays can establish sensitivity for these allergens. LMW agents, such as platinum salts, combined with proteins that act as haptens can also result in the production of IgE antibodies that can be used for testing even though their usefulness is controversial. Trimellitic anhydride acts through various mechanisms including IgG, IgE and irritant [5]. An IgE RAST score of three or greater has high specificity for isocyanate-induced asthma [6].

OA due to other LMW agents likely act through inflammatory mechanisms by damaging airway epithelium leading to a cascade of proinflammatory cytokines and chemokines. These molecules recruit and activate a wide variety of cells ultimately leading to airway inflammation with subepithelial fibrosis. Another mechanism is nonspecific histamine release from mast cells in the respiratory tract, which can lead to OA in workers inhaling cotton bract, flax and soft hemp [7].

Despite the pathophysiologic mechanism, inflammation contributes to BHR and through airway remodeling or airway smooth muscle contraction leads to airflow obstruction resulting in complaints from workers of wheezing, coughing, chest tightness and/or shortness of breath.

Epidemiology

Despite the increased appreciation of asthma through practice parameters, treatment guidelines and the popular press, OA remains under-diagnosed and therefore under-treated. Reasons for this include difficulty in establishing the diagnosis accurately, lack of clear associations between workplace exposures and symptoms, and the variable nature of asthma. The most common type of OA is the immunologic type mediated by IgE and accounting for 93% of cases, while 7% of cases are attributed to irritant or non-IgE-mediated mechanisms [8].

The estimated prevalence of OA and the risk for specific sensitizing agents is variable and may be related to the definition of OA used and type of study performed such as population-based compared with workplace-based. Workplace-based studies may lead to underestimations due to the 'healthy-worker effect'. This bias occurs when ill workers leave the workplace without indicating to their employer a causal relationship to work. Using US National Health and Nutrition Examination Survey (NHANES) data between 1988 and 1994, the estimated prevalence of work-related asthma was 3.7% and work-related wheezing 11.5% [9]. When the NHANES data was reanalyzed for specific job title, the highest risk group was workers exposed to cleaning chemicals [10]. Health-related occupations and sales workers constituted the highest number of cases but had low risk in terms of odds ratios. The population attributed risk reached 26% [10].

The definition of asthma and the definition of exposure both affect the strength of the association when evaluating OA when using a population-based approach. The more specific the exposure, timing of the exposure and asthma definition, the higher the odds ratio that was obtained when a survey of over 14,000 French adults from 1975 was analyzed [11]. Using measures, such as job title and self-report of symptoms alone, can be misleading by either over- or under-estimating sensitizing agent exposure and may be prone to recall bias. Furthermore, the prevalence of self-reported OA occurred in areas with a higher community prevalence of asthma and when pooled analyses combined different areas with varying rates of asthma [12].

Data from industry-based studies, surveillance and case studies have identified over 400 different workplace exposures that are associated with asthma [1]. Isocyanates are the most frequently cited chemical that relates to OA. This broad category includes toluene diisocyanate (TDI), diphenylmethane diisocyanate, 1,5-Naphthylene diisocyanate, isophorone diisocyanate and prepolymers of these compounds. TDI is a key component in the production of polyurethanes used in adhesives, foams, varnish and industrial paints. A more recent example of diisocyanate exposure was found workers installing truck bed liners leading to the release of State Hazard Alerts [101].

In the past two decades, work-related asthma in healthcare workers has focused on natural rubber latex allergy. Analysis of surveillance data from four states from 1993–1997 indicate that cleaning chemicals used in hospitals, practitioners offices and specialized nursing facilities now constitute the most prevalent trigger ahead of latex [13]. Natural rubber latex gloves and products have been replaced with nonpowdered latex or synthetic latex gloves and products in many institutions. Cleaning products, including disinfectants, such as quaternary ammonium compounds, are commonly used for surface cleaning in clinical and food preparation areas. Cleaning products can also contain irritant chemicals such as bleach, ammonia and hydrochloric acid. Use of these cleaning products occurs in industrial and nonindustrial settings and their use exposes workers whose primary job is to use them in addition to workers exposed while these chemicals are being used in their work areas [14,15].

Box 1. Screening questions for occupational asthma

- What kind of work do you do?
- Are you exposed to chemicals, dust or fumes at work?
- Are your symptoms worse at work and better on weekends and vacations?
- Do you think your health problems are related to work and if so, why
- Did your symptoms change when your job changed or a new product or process was introduced?

Follow-up questions if affirmative answers to the above questions.

- Do your symptoms worsen over the course of the week and at night on workdays?
- Are there tasks at work that you avoid because they worsen your breathing?

Symptoms may occur after inappropriate mixing or after prolonged exposure in areas with poor ventilation, and not necessarily in relation to product spillage. A variety of occupations have been identified as having increased risks for developing OA including detergent factory workers [16], construction workers [17] and hair dressers [18].

Available diagnostic & therapeutic approaches**Diagnostics**

The diagnosis of OA should begin with confirmation that the patient indeed has asthma. This should be established objectively and all asthma triggers identified. A small number of probing questions may be used to screen for an occupational component (BOX 1) prior to obtaining a detailed and comprehensive occupational history. Exposures to a sensitizer or aggravating factor should be ascertained. The history should focus on the details of the job with attention paid to frequency and intensity of exposures to potential causal agents. The reliability of questionnaires in the diagnosis of OA may provide sensitivity of up to 92% but low specificity (14–32%) [2]. Since many workers may be unaware of chemicals they are exposed to, additional information can be obtained from Material Safety Data Sheets that are required to be present for workplace chemicals by law. The relationship between asthma and work can then be evaluated and established. Early on, symptoms may occur after exposure at the workplace and resolve completely with avoidance on weekends or vacations. It is at this time that the occupational relationship can be more easily established and with intervention prevent worsening of symptoms. Over time with continued workplace exposure, symptoms may only partially abate when away from the workplace or become continuous without a clear pattern. When symptoms are of delayed-onset, a work-related pattern can be difficult to elicit. The diagnosis of asthma is confirmed when there is a compatible history with evidence of reversible airway obstruction or in the presence of normal lung function, BHR as measured by provocative challenge with methacholine or histamine. The dose of inhaled methacholine (provocative concentration) that reduces the forced expiratory volume (FEV)₁ aspect of lung function by 20% is termed the PC₂₀. The lower the PC₂₀, the higher the BHR. The PC₂₀ FEV₁ has arbitrarily been set at 8–16 mg/ml

and is highly sensitive [19]. A negative test for BHR has a strong negative predictive value, although cases of diisocyanate-induced asthma have been reported with normal methacholine test results. This may have been related to the avoidance of exposure for even a few hours. Annual methacholine challenges may offer insight as to the prognosis since permanency is associated with persistent evidence of BHR. A three-fold or greater decline in BHR after avoidance of the workplace suggests OA rather than aggravation of pre-existing asthma [2].

Other causes for chronic or recurrent cough, dyspnea and wheezing should be ruled out including gastroesophageal reflux, congestive heart failure, paradoxical vocal fold motion, inhaled foreign body, tumor, chronic obstructive pulmonary disease, sinusitis and sarcoidosis [102]. Some patients may develop rhinoconjunctivitis prior to asthma particularly with HMW antigens [20]. A site visit by an individual qualified in industrial/occupational hygiene may help identify triggers and obtain environmental exposure levels.

Serial peak expiratory flow (PEF) measurements four-times daily for 4 weeks are recommended for objective confirmation of suspected occupational asthma. This approach was superior to FEV₁ [21]. This information at work and away from work along with symptoms and medication usage may be particularly useful. The use of peak flow records to document decrements in lung function across work-shifts has been useful but hampered by motivation and dedication from the patient in providing sufficient data points. Also, data accuracy can be problematic if workers are fabricating data, have poor effort in peak flow technique or the peak flow meters are inaccurate. Computer-assisted analysis of peak flows has a sensitivity of 73–86% and specificity of 74–100% [22]. Workers who received specific instructions from a peak flow specialist and recorded their data on a dedicated occupational form had better return rates and data quantity compared to patients instructed through the mail or reviewing pre-existing peak flow diaries from other clinics. The most common reason for incomplete PEF records was data on less than three consecutive days at work.

While specific inhalation challenge tests to occupational agents may be considered the ‘gold standard,’ they are not common practice as they are labor and time intensive requiring trained personnel and only offered in a few specialized centers [23]. When

performed, various patterns of responses may be observed including isolated immediate responses within minutes, a dual response that includes the immediate response followed by a decrease in FEV1 at 4–6 h or a late response at 4–6 h only. It appears that an isolated late response is more common in OA [2]. Since both false positive and false negative results can occur, inhalation challenge tests are generally reserved for cases where a new occupational antigen is suspected, when the diagnosis is still uncertain after the usual evaluation or when there is discrepancy between objective measures of lung function.

Immunologic tests are less useful owing to the lack of standardized and commercially available agents used for both skin testing and *in vitro* IgE assays particularly for LMW agents. Some of these tests are only well standardized in a few academic centers, limiting their widespread use. Furthermore, biomarker tests (specific antibodies) that indicate exposure may not represent disease. Diisocyanate-induced asthma (spray painters) appears to be mediated by either IgE-mediated inflammation or non-IgE-mediated mechanisms [24]. Asthma related to TDI appears to be associated with oxidative stress in the airway lining after formation of conjugates of isocyanates and lung epithelial proteins. While glutathione activity in the lung protects against oxidative stress, allelic variants, including the null genotype of the glutathione-S-transferase enzyme, are associated with an increased risk of developing TDI asthma [25,26]. A study using biomarkers including mRNA for C ϵ , interleukin (IL)-4, IL-5, CD25⁺ and CD4⁺ cells found a striking absence of C ϵ and IL-4 mRNA in bronchial tissue after an inhalation challenge with diisocyanate suggesting that IgE is not necessarily associated with the induction of OA by diisocyanates in workers with undetectable serum-specific IgE to diisocyanates [26].

Alternative methods to assess airway inflammation include invasive methods, such as bronchoscopy with bronchoalveolar lavage and biopsy, or noninvasive methods, such as induced sputum (for eosinophilia, eosinophilic cationic protein or eotaxin) and exhaled nitric oxide (eNO). Many factors that can influence eNO levels, such as inhaled steroids, smoking, nitrate-containing foods, respiratory infections and eNO produced from the stomach and sinuses, prevent its widespread acceptance as a useful test at this time [2]. Other noninvasive tests to measure airway inflammation under evaluation include levels of isoprostanes, aldehydes, prostaglandins and leukotrienes in exhaled breath condensate samples [2]. Since serial measurements can be made quickly and easily, these may offer additional useful tools in evaluating OA.

Optimal therapy

The optimal management for OA, as in other allergic disorders, is identification and avoidance of the specific inciting agent/trigger. In a broader sense, prevention can occur as primary (prevent sensitization), secondary (early detection of sensitization before permanent disease occurs) and tertiary (limiting medical impairment once disease has occurred) (TABLE 1) [27,28].

Primary prevention entails avoiding sensitizers and hazards that are known to induce disease. In OA, such prevention may

include eliminating the source of exposure by substituting with a different product. An example of successful primary prevention is the substitution of powdered latex gloves with synthetic or low-protein nonpowdered latex gloves, thereby decreasing the risk for healthcare workers [29,30]. If a nonhazardous substitution for the inciting agent is not available, then changes in engineering controls, manufacturing processes or work practices, including enclosing the industrial process or optimizing ventilation systems, may be helpful. Generally this type of prevention is outside the control of the clinician and requires policy changes by management but is supported by scientific evidence. Personal respiratory protection may decrease exposure but requires professional guidance for correct size and fitting. While it is important for the worker to understand the importance of wearing a respirator, the onus is on the employer to correct a situation where there is overexposure to the sensitizing agent. Variable results have been observed with the use of personal respirators and they are not intended to become a suitable permanent solution to minimize workplace exposures. Two workers with confirmed OA to buckwheat and wheat obtained complete protection at work for 2–3 years by wearing a dust respirator (3M-disposable dust respirator No 9920, Shigematsu, Tokyo). However, it was not reported if spirometry normalized or nonspecific BHR improved [31]. Dairy farmers using powered dust respirator helmets had improved symptoms [32], while aluminum pot-room workers symptoms were unchanged, but peak expiratory flow rates improved [33]. In red cedar asthma, twin cartridge respirators were associated with better outcomes than air-stream helmets [34]. Another example would be employee education programs that focus on alerting workers to factors that could increase their risk of developing OA.

The prognosis for OA is worse than that for non-OA due in part to the fact that workers remain in their jobs and continue to be exposed [35–37]. Unfortunately, even avoidance of further exposure does not ensure complete recovery. Depending on the occupational agent, only half of workers with OA will go into remission after occupational exposure to the sensitizing agent has ceased [38]. Some workers may have to change job locations or be retrained for jobs without exposure to the inciting agent. Other irritant exposures should be decreased or eliminated including tobacco smoke. A prospective observational study in Scotland established that bar workers with asthma had reduced airway inflammation and improved quality of life after the prohibition of smoking in confined public places [39]. However, a review of the published literature reveals contradictory results for tobacco smoke inciting OA [40]. Smoking may be a determinant of OA due to HMW allergens such as snow crab and salmon processing industries, latex and detergent enzymes [40]. Data was contradictory for smokers who developed laboratory animal allergy and no significant association has been found between smoking and OA due to LMW agents [40]. By contrast, repeated ozone gas exposures that result in respiratory symptoms in bleachery workers in Swedish pulp mills resulted in higher exhaled nitric oxide levels and increased prevalence of asthma and wheezing [41].

Table 1. Strategies to prevent occupational asthma.

Prevention	Measure	Selected examples
<i>Primary</i>		
	Inform potential workers of worksite sensitizers and irritants	Worker education program
	Rotate employees	Rotate between jobs with sensitizer exposure to limit total exposure below PEL*
	Decrease number of employees exposed	Decrease work shift, number of workers per shift or increase rest periods
	Identify highly susceptible workers	Genotype GSTP1 in TDI asthma MHC for animal-induced asthma and platinum
	Limit exposure to respiratory irritants	Change position of worker relative to emissions Avoid ozone and tobacco smoke if exposed to HMW agents or if pre-existing asthma
	Avoid respiratory sensitizers	Choose a chemical with a lower evaporation rate or vapor pressure; synthetic latex
	- Substitute with safer or chemically modified agent	Choose chemicals without hazardous ingredients
	- Monitor airborne levels of emissions	Industrial hygiene: personal and job location monitoring for inhalants and skin absorption
	Modify work methods	Mechanical fans or allow natural air movement to create adequate airflow through an area
	- Improve general ventilation to dilute and remove emissions	Build an enclosure around a process (blasting cabinet or laboratory hood)
	- Enclose a process	Paint dipping or rolling instead of spraying
	- Change a process	Bolt an item instead of welding
	- Reduce and remove emissions	Encapsulate detergent enzymes
	Personal respiratory protective equipment	Robotics or automate a process Install exhaust hoods to capture emissions Wear properly fitting masks, gloves, goggles and coveralls; air supply helmet respirator
<i>Secondary</i>		
	Medical surveillance:	Diisocyanates, enzymes, platinum exposures
	- Periodic questionnaires, spirometry	Platinum salts and HMW agents Th2 cytokine fingerprinting
	- Allergy skin tests	Antigen-stimulated monocyte chemoattractant protein-1 synthesis for TDI asthma
	<i>In vitro</i> tests	Self report and report coworker symptoms
	Education	CME courses in OA
	- Improved worker education: early reporting of symptoms	Screening questions and complete history
	- Improved physician education for early recognition	Referral centers and worldwide databases
	- Improved physician resources	
<i>Tertiary</i>		
	Separate employees from areas of emission and sources	Use a control room Avoid immunologically cross-reacting agents
	Reduce exposure**	Air supply helmet respirator
	Medical monitoring: symptoms, medication need, peak flows, spirometry, BHR and ?FeNO	Any occupation with sensitizer or irritant exposure
	Asthma pharmacotherapy	SABA, ICS, LTM, LABA, oral steroids and anti-IgE?
	Disease modification	Specific allergen immunotherapy

* Some specific rules may prohibit the use of this control method.

BHR: Bronchial hyper-responsiveness; FeNO: Fractional exhaled nitric oxide; GSTP: Glutathione S-transferase-placental form; HMW: High molecular weight; ICS: Inhaled corticosteroids; Ig: Immunoglobulin; LABA: Long-acting inhaled β -agonists; LTM: Leukotriene modifier; MHC: Major histocompatibility complex; OA: Occupational asthma; PEL: Permissible exposure limit; SABA: Short-acting inhaled beta-agonists; TDI: Toluene diisocyanate; Th: T helper.

Secondary prevention refers to early identification of employees sensitized, but not yet symptomatic. This type of prevention

may include monitoring lung function, allergy skin testing or *in vitro* specific IgE assays and the use of questionnaires for

employees in workplaces with known sensitizers. If an index case presents, additional workplace exposures should be evaluated to identify other exposed and potentially sensitized or affected workers. Spirometry used in conjunction with questionnaires can identify diisocyanate workers earlier at a younger age and with milder OA resulting in improved prognosis [42]. A positive skin test for platinum salts in workers exposed to these compounds is highly predictive of developing occupational asthma. These workers would then need to be removed from exposure [43]. Skin test conversion to negative within 6 months after removal from exposure correlates with resolution of the work-related respiratory symptoms. A history of atopy or cigarette smoking may increase the risk of sensitization for OA due to HMW antigens, platinum salts and anhydrides [2].

Tertiary prevention is defined as preventing additional injury to an already sensitized and symptomatic worker. Methods include avoidance and pharmacologic therapy that is not different from that for non-OA. Early intervention and treatment for inflammation may be the key to successful outcomes; however, a systematic review of the literature found that even after cessation of exposure symptomatic recovery varied from 0–100% with a pooled estimate of 32% [44]. Persistent BHR at follow-up was 73% and higher in workers sensitized to HMW agents. Workers with a duration of exposure less than 76 months had the highest rate of recovery. The potential for bias in the studies reviewed was high and likely underestimates the true rate of recovery. Allergen injection immunotherapy has been attempted in latex allergic patients without a significant improvement in symptoms [45].

Factors likely to affect choice of therapy or patient response or compliance

Owing to labor market circumstances, a job change is not always possible. This has led to workers continuing to be exposed to their specific triggers. In a longitudinal uncontrolled study of 20 adults with mild to moderate persistent OA (15 whom were carpenters), ten continued to work in their job [46]. After 3 years, regular treatment with inhaled corticosteroids and long-acting bronchodilators prevented deterioration in the respiratory status as measured by lung function, symptom scores, peak flow variability and BHR of those who continued working. Other studies have evaluated workers with OA who have persistent exposure for 1 and 6.5 years and results ranged from no deterioration in asthma to 40% deterioration in asthma respectively [47,48]. Although a careful analysis of the risks and benefits is required when making recommendations on continued exposure at the worksite, it is paramount to pursue all options to significantly decrease and if possible eliminate ongoing exposure to the implicated agent.

Expert commentary

Although asthma is a high profile disease state and receives much attention in the form of epidemiology, pathophysiology and pharmacotherapy, the subpopulation of OA tends to be overlooked, under-reported and under-treated. A review of records of adult-onset asthma revealed a discussion of work exposures in only 7% of cases, underscoring the fact that physicians frequently do not

ask about a patient's work [49]. Diagnosing OA requires more time in terms of detail in documenting all occupational exposures, may include a site visit and coordination of care with others including pulmonologists, industrial hygienists, occupational physicians and attorneys. During physician training programs, much emphasis is placed on hospital care of patients with asthma, leaving few opportunities in a busy clinic to become proficient in the evaluation of OA. For primary care physicians, OA may not have been part of the curriculum and the large number of patients generally seen in out-patient clinics imposes on the time required to evaluate a patient for suspected OA.

The level of comfort of asthma experts including pulmonologists and allergists varies in terms of assessing OA. This may stem from lack of depth and breadth of exposure during fellowship training, comfort of mentors during training or lack of emphasis in the curriculum. After entering practice, the unavailability of specialized testing equipment, apprehension of advocating for patient compensation during legal proceedings and preparation of documents or the sheer lack of time that can be committed to a small number of patients may deter even specialists from pursuing OA evaluations. Clinicians may feel uneasy about interpreting industrial hygiene evaluations that uses language such as permissible exposure limit, threshold limit values, time-weighted average values, and short-term exposure limits or ceiling limits. Preparing documents that require assessments of disability (relative estimate of health status as assessed by patient and physician) and grading impairment (a functional decrement) using terms such as permanent or temporary that have medicolegal implications can be met with trepidation. Some clinicians may be unaware of which academic or specialized centers are capable of conducting occupational evaluations. Evaluations for suspected OA can be frustrating in terms of obtaining accurate and specific information on workplace substances and exposures, documenting the specific trigger and navigating the complex system of and knowing the roles of workers, unions, management, NIOSH and OSHA.

New clinical strategies

Worker & management education

Even if companies engage in obligatory monitoring of workers who are exposed to known sensitizers to identify sensitized employees early, this doesn't prevent sensitization and is therefore a failure of primary prevention. When a new chemical whose sensitization potential is unknown is being introduced, good work practices should be employed early rather than wait for a sentinel event to occur. In all cases, monitoring of environmental exposures and airborne levels of agents should be performed. If levels exceed permissible limits, measures can be undertaken. High risk workers should be educated regarding risk factors for developing OA. Unfortunately, with a high proportion of the general population being atopic, counseling atopic patients to avoid exposure to HMW agents is not practical. New building technologies should continue to focus on improved heating, cooling and ventilation systems that reduce irritant and sensitizer exposures. Attention should be paid to

small employers who may not have the expertise or infrastructure comparable to large employers. New and rapidly expanding industries that use potentially hazardous chemical/agents may benefit from targeted inspections by agencies such as state department of labor and industries to assess compliance with safety and health regulations.

Physician Education

Continuing medical education venues on OA should be aimed at practicing physicians and training programs for residents to increase the awareness and importance of early recognition and referral to an OA specialist to improve outcomes. This may include changes in the teaching curriculum in primary care as well as subspecialties.

Pharmacotherapy

Current treatment of asthma focuses on preventing inflammation. Therefore at every level of persistent asthma inhaled corticosteroids are recommended, the dose being adjusted according to asthma severity with higher doses recommended for more severe asthma. Various inhaled steroids (fluticasone, budesonide, mometasone, beclomethasone, triamcinolone and flunisolide) are available in assorted delivery systems (dry powder inhaler vs pressurized metered dose inhaler vs jet nebulizer) that can be employed. The importance of proper inhaler technique is paramount in delivery of the medications to the peripheral airways. Long-acting inhaled beta-agonists (LABA) have been recognized to be steroid-sparing and therefore used in combination with inhaled corticosteroids in moderate to severe persistent asthma. US FDA warnings on the risks of LABA should be discussed with each patient [103]. Leukotriene modifiers, such as montelukast, zafirlukast and zileuton, also reduce inflammation and are considered alternative controller medications or add-on therapy to inhaled corticosteroids. Theophylline continues to be a controller therapy although the therapeutic index is narrow and drug interactions are common, therefore necessitating monitoring serum levels. Allergen immunotherapy for HMW allergens is currently the only disease modifying strategy for allergic asthma. In the context of OA, this has only been studied for natural rubber latex and asthma symptoms were not improved [45]. New therapies directed at the control of asthma include injection of

monoclonal antibodies directed against IgE. While omalizumab has shown efficacy in allergic asthma in both adults and children, specific studies in OA are lacking. As in non-OA, short-acting inhaled beta-agonists (SABA), such as albuterol, are reserved for acute relief of symptoms. Overuse of SABA is an indication of uncontrolled asthma and requires additional investigation.

Desirable further improvements

A directory or listing of institutions, academic centers or clinicians with expertise in the diagnosis and management of occupational respiratory disease would be an important and useful resource for primary care physicians and other specialists who are not fully equipped to perform such evaluations. A partial listing of centers that offer selected specialized clinical tests in evaluations of environmental and occupational disease is available on the American Thoracic Society website [104]. Currently, a list of centers and clinicians with their areas of expertise is being generated by the occupational respiratory disease committee of the American Academy of Allergy, Asthma and Immunology to be posted on their website.

Five-year view

In 5 years there should be significant advancements in the diagnosis and treatment of OA, including:

- More research focused on irritant-induced asthma examining all aspects of asthma aggravated by the workplace;
- Knowledge on the epigenetics (environment–gene interactions) for OA;
- Knowledge of a chemicals potential for sensitization before entering the workplace;
- Developing standards for maximum concentrations for key occupational allergens to lower exposure;
- Worldwide databases to monitor trend in frequency and nature of occupational agents;
- Simple and affordable means of surveillance to identify and characterize OA cases early;
- Widespread use of objective means to correctly diagnose OA early;
- Assess and address socioeconomic impact of OA and revisit methods of assigning permanent disability [50].

Key issues

- Occupational asthma (OA) is under-recognized and potentially difficult to diagnose.
- Many physicians are uncomfortable with managing patients with OA owing to the complexities and time involved.
- Treatment options are limited to current pharmacotherapy for asthma, most of which have not been specifically studied in OA and, most importantly, avoidance of the occupational agent.
- The particular agent may be difficult to confirm and even more difficult to avoid leading to significant upheaval for the affected worker and company.
- Primary, secondary and tertiary prevention measures should be employed and individualized for workers, allergens/agents and worksites/industries.
- On the horizon are methods that promise to improve our ability to diagnosis and treat OA.

Improving the education of physicians is an ongoing mission of the parent societies and boards. Changes in curriculum can be adopted as these unidentified needs are revealed. Electronic medical records that have patient intake forms that include detailed pertinent occupational information may more quickly identify adults with asthma that have an occupational trigger.

Genetic markers of OA are already being explored. A genetic predisposition may modify or confound an individual's response to a particular sensitizing agent. Genotyping specific for the major histocompatibility complex genes on chromosome 6p may eventually be available on a routine basis. Human leukocyte antigen (HLA) associations, such as HLA-DR β 1*07, have been identified for rat antigens in individuals working in an animal housing facility and in workers exposed to complex platinum salts [51].

Using an animal model, cytokine fingerprinting showed a T-helper 2 cytokine production pattern with occupational sensitizers such as acid anhydrides, diisocyanates, glutaraldehyde and complex platinum salts after the rats underwent skin

exposure before they exhibited respiratory symptoms [52]. If human sensitization is similar to these animal studies, screening for occupational respiratory chemical sensitizers using skin tests may become applicable. Testing for diisocyanate asthma using antigen-stimulated monocyte chemoattractant protein-1 synthesis is better than assay of specific antibodies [53]. The widespread use of noninvasive methods that assess lung inflammation, including fractional exhaled nitric oxide, should become more widely available at a lower cost. Improved immunologic assessments will undoubtedly be developed to accurately diagnose sensitization to specific agents. Improved avoidance techniques in factories may include automated workstations, robotics, personal respiratory monitoring and improved ventilation with dust control.

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- Lists of centers that offer selected specialized clinical tests in environmental and occupational evaluations.

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