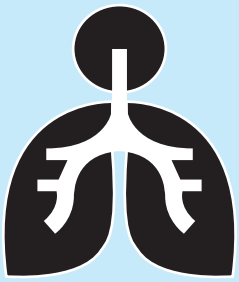
Asthma Focus

Key Points



Work exposures can cause or exacerbate asthma and can also be associated with asthma variants (e.g., eosinophilic bronchitis and aluminumpotroom asthma) as well as symptoms that mimic asthma (e.g., the irritable larynx syndrome). In addition, even non-work-related asthma can affect the ability to work. This article focuses on current data about occupational asthma, defined as asthma due to conditions attributable to work exposures and not to causes outside the workplace.

Work-related asthma (WRA) encompasses work-exacerbatedasthma (bronchospasm aggravated by work exposures in patients with concurrent or pre-existing asthma) and occupational asthma (asthma caused by exposures to sensitizers or allergens at work). Occupational asthma (OA) is defined as "adisease characterized by variable airflow limitation and/orhyper-responsiveness and/or inflammation due to causes andconditions attributable to a particular occupational environmentand not to stimuli encountered outside the workplace"

Occupational asthma

Occupational asthma can be caused by a specific workplace sensitizer, defined as an agent that induces asthma through a mechanism that is associated with a specific immunologic response. Occupational sensitizers are commonly high-molecular-weight agents (>10 kD, usually a protein or glycopeptide) that can cause production of specific IgE antibodies and typical allergic responses. Once a person is sensitized, very low exposures can induce asthma, which is often associated with rhino-conjunctivitis. Common examples are listed in Table 1. New causative agents are reported each year, and it would appear that almost any protein that becomes airborne and inhaled might be a potential cause of occupational asthma.

Low-molecular-weight occupational chemicals can also cause sensitization and, subsequently, asthma. A few have been associated with the production of specific IgE antibodies, such as complex platinum salts used in platinum refineries or the manufacture of catalysts, with a recent report of cases in workers exposed to platinum salts during the manufacture of cytotoxic drugs. Other examples include rhodium salts (used in electroplating); salts of nickel, chrome, and cobalt; acid anhydrides (used as hardeners in epoxy resins in chemical plants and in powder paints); and reactive dyes (used in textiles).

However, most low-molecular-weight chemical sensitizers induce asthma through mechanisms that are poorly understood, despite a phenotype suggesting sensitization. Diisocyanates are important sensitizers that are used in the production of rigid or flexible polyurethane foam; they are also used as hardeners in urethane spray paints and adhesives. Diisocyanates have been the most common cause of occupational asthma in many industrialized areas. Other examples of low-molecular-weight sensitizers are listed in Table 1. Most chemical sensitizers have highly reactive side chains.

Non-sensitizing, Irritant-Induced Occupational Asthma

Irritant-induced occupational asthma is a term used to describe occupational asthma that occurs from exposure to agents considered to be airway irritants, in the absence of sensitization. In 1985, diagnostic criteria for the reactive airways dysfunction syndrome, a severe form of irritant-induced asthma, were introduced (Table 2). Subsequent reports have modified the initial, stringent diagnostic criteria for this syndrome and use the term "irritant-induced asthma" to include cases with induced airway symptoms and an onset after one or more high-level exposures. This category also includes cases with less immediate responses to exposure (Table 2), with the recognition that these latter cases have less diagnostic certainty.

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Table 1: Common Causative Agents in Sensitizer-Induced Occupational Asthma

Agent	Workers at Risk of Exposure
High-molecular-weight agents	Farmers, persons who work with laboratory animals, veterinarians
Animal allergens	Greenhouse workers, farmers
Plants	Latex-glove makers and users, makers of other latex products
Plant products (e.g., natural rubber latex)	Farmers, grain workers, bakery workers
Cereals and grains	Food-production workers, cooks
Other foods (e.g., milk powder and egg powder)	Office workers, laboratory workers
Fungi	Laboratory workers, pharmaceutical workers, bakery workers
Enzymes	Farmers, greenhouse workers
Insects	Workers handling herring or snow crabs
Fish and crustaceans	Printers, including carpet makers
Vegetable gums (e.g., guar and acacia)	
Low-molecular-weight agents	Makers of rigid or flexible polyurethane foam, installers of polyurethane foam insulation, urethane spray painters, those who work with urethane adhesives or urethane molds in foundries
Diisocyanates (e.g., toluence diisocyanate, hexamethylene diisocyanate and methylene diphenyl diisocyanate)	Makers of epoxy resins for plastics
Acid anhydrides (e.g., phthalic anhydride, maleic anhydride and trimellitic anhydride)	Chemical-industry workers, dental workers, aestheticians applying artificial nails
Acrylic monomers	Carpenters, sawmill workers, forestry workers
Wood dusts (e.g. from red cedar and exotic woods)*	Refinery workers, jewelry workers
Complex platinum salts	Metal-plating workers, welders of stainless steel
Other metal salts (e.g., nickel chromium)	Health care workers
Biocides (e.g., glutaraldehyde and chlorhexidine)	Makers of wood products, foundry workers
Phenol-formaldehyde resin	Hairdressers
Persulfates and henna	Pharmaceutical workers pharmacists
Drugs (e.g., antibiotics)	Lacquer handlers, soldering workers, spray painters, professional cleaners
Aliphatic anines (e.g., ethylenediamines and ethanolamines)	

* Wood dusts can contain low-molecular-weight sensitizers, such as plicatic acid in red-cedar dust, but can also cause sensitization and promote the production of specific IgE antibodies to high-molecular-weight components

The possibility that relatively low concentrations of airborne irritating chemicals at work could induce asthma (termed by some authors "not-so-sudden asthma" or "low-dose reactive airways dysfunction syndrome") has been considered in case reports and small case series. However, the association with previous atopic disease or childhood asthma and the long-term low-level exposure in some cases raised the possibility that symptoms may have resulted from exacerbation of underlying airway hyper-responsiveness or coincidental onset of asthma, rather than occupational asthma itself. Nevertheless, more recent support for the concept that exposure to relatively low concentrations of chemicals at work may induce asthma comes from several epidemiologic studies involving groups of workers exposed to irritant agents such as cleaning products and air fresheners. Workers with an increased risk of asthma associated with exposure to irritants under usual work conditions include cleaners (domestic and industrial cleaners), nurses, textile workers, hog farmers, poultry workers, and aluminiumpotroom workers (in aluminium smelters). Thus, a spectrum of exposures leading to asthma seems likely, although asthma induced by exposure to low-level irritants cannot be reliably diagnosed in individual workers at present. Similarly, increased risks of asthma (in some cases with concomitant symptoms of bronchitis or with COPD) have been associated with irritant exposures without clear features of sensitization - for example, among entertainment workers, other farmers (with exposures to ammonia, endotoxins, and organic dusts associated with livestock), and motor vehicle operators.

Epidemiology:

Occupational asthma has been reported in a minority of workers exposed to most known sensitizing agents (usually 10% or less among current workers in cross-sectional studies). In addition to the inherent sensitizing potency of a given agent in the workplace, the level of exposure influences the rate of

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sensitization, as shown with both high-molecular-weight sensitizers such as animal proteins (in persons who work with laboratory animals) and flour proteins (in bakers) and low-molecular-weight sensitizers such as diisocyanates. For example, workplaces with exposure to lower concentrations of diisocyanates have lower rates of occupational asthma. Predisposing or host factors among workers have included atopy (for most high-molecular-weight sensitizers), other genetic factors, and, possibly, smoking. None of these factors are sufficiently predictive to be used in determining the ability of a worker to participate in a job that carries a risk of sensitization.

Table 2: Features of Irritant-Induced Occupational Asthma.

Criteria for RADS*	Modifications to Criteria for RADS†
History of new-onset asthma	History of new-onset asthma or recurrence of childhood asthma
Symptom onset related to a single high-level exposure (usually accidental)	Symptom onset related to one or more high-level exposure
Onset of symptoms ≤24 hr after exposure	Symptoms can begin >24 hr (in some reports, up to several days) after exposure
Exposure to a very high concentration of gas, fume or spray with known irritant properties	List of exposures includes highly irritating dust (e.g., after the World Trade Center collapse)
Airway hyperresponsiveness or reversible airflow obstruction	
Symptoms persistent for ≥3 mo	
No previous lower respiratory tract symptoms	Previous airway disease associated with smoking or atopy may be difficult to rule out

Population studies in a number of geographic regions have estimated the incidence and prevalence of occupational asthma caused by exposures to sensitizers and irritants. Although true geographic variation appears to be present, differences in study methods render comparisons difficult, as recently observed. A study involving almost 7000 participants in 13 countries used uniform methods to identify new-onset asthma and showed that the population attributable risk of occupational asthma was between 10 and 25%, equivalent to an incidence of 250 to 300 cases per 1 million people per year. Risks were increased among workers with known exposure to respiratory sensitizers. A systematic analysis of population attributable risk showed that an estimated 16.3% of all cases of adult-onset asthma are caused by occupational exposure. There is a discrepancy between the rates of asthma diagnosed by a health professional as being work-related (4.7% of all new asthma cases) and rates that include self-reported cases of work-related asthma (18.2% of all new asthma cases); one possible explanation for the difference is that occupational asthma is under-recognized in clinical practice.

Fewer studies have examined the prevalence or incidence of irritant-induced asthma with the use of the original criteria for the reactive airways dysfunction syndrome. A small study conducted after glacial acetic acid was spilled in a hospital showed a clear exposure-response relationship: the incidence of asthma was highest among those with the greatest exposure (four of nine persons without previous respiratory symptoms). An association with the level of exposure was also found for the development of airway hyperresponsiveness and asthma and for other outcomes among responders to the World Trade Center disaster. The multinational survey noted above showed that workers who reported an acute symptomatic inhalation event (e.g., exposure to a chemical spill) had an increased risk of new-onset asthma (relative risk, 3.3; 95% confidence interval, 1.0 to 11.1; P=0.05).

Pathophysiological mechanisms:

The pathophysiological mechanisms of occupational asthma appear to be similar to those of non-work-related asthma, including an IgE-dependent mechanism associated with high-molecular-weight sensitizing agents and some low-molecular-weight sensitizers. However, for asthma induced by other low-molecular-weight sensitizers, such as diisocyanates, and for irritant-induced asthma, the mechanisms are incompletely delineated. Nevertheless, occupational asthma constitutes an important model for an improved understanding of both extrinsic and intrinsic factors in non-work-related asthma. Mechanisms involved in sensitizer-induced asthma and irritant-induced asthma are shown schematically in Figure 1.

Diagnosis

Sensitizer-Induced Asthma: Occupational asthma should be suspected in every adult with new-onset asthma. Although the respiratory symptoms in cases of occupational asthma, such as wheezing, dyspnea, chest tightness, cough, and sputum production, are similar to those in cases that are not work-related, their occurrence is usually modulated by the work-related exposure.

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A latency period ranging from weeks to years after the first exposure to the sensitizer is observed before the initial onset of work-related symptoms.

Sensitizer-induced symptoms begin variably - at the beginning of the work shift, toward its end, or even in the evening after working hours. Typically, remission or improvement occurs during weekends and holidays. Rhinitis often accompanies or precedes lower respiratory symptoms, especially when high-molecular-weight agents incite the asthma. Although a thorough clinical and occupational history must be obtained, a compatible history alone is insufficient for diagnosis and has a low positive predictive value. Investigations should be started as soon as the diagnosis is suspected, preferably while the patient is still working, and should be as comprehensive as feasible, including assessment of clinical symptoms, objective confirmation of asthma, testing for skin or serologic specific IgE antibodies when possible, and documentation of symptomatic, functional, and inflammatory changes in response to exposure to occupational agents (at work vs. away from work or by specific challenge). Each test has limitations that may be overcome by combining several tests. A suggested diagnostic approach is summarized in Figure 2.

Irritant-Induced Asthma: Diagnosis of irritant-induced asthma relies on a suggestive clinical history along with the demonstration of airflow limitation or airway hyper-responsiveness. The diagnostic criteria are described in Table 2. Primary, secondary, and tertiary preventive measures may reduce the incidence and severity of sensitizer-induced asthma (Table 3).

Prevention and Management

Sensitizer-Induced Asthma: Primary prevention aims to prevent sensitization to workplace agents, thus preventing disease. Ideally, the workplace would have measures in place so that workers do not inhale agents that can cause asthma. One way to achieve this aim would be to replace known sensitizing agents with non-sensitizers - for example, by replacing gloves made of natural rubber latex with nitrile gloves. In the case of chemical sensitizers, a computer program that uses a quantitative-relationship model may have some ability to predict risks when new, potentially sensitizing agents are under consideration for use in the workplace. Unfortunately, many sensitizers cannot be readily replaced with nonsensitizing agents (e.g., flour in bakeries). However, a reduction in exposure (inhalational exposure and possibly also skin exposure) to a respiratory sensitizer can reduce the proportion of workers who become sensitized. Efforts have been made to reduce exposure to respiratory sensitizers by instituting occupational hygiene measures such as containment, improved ventilation, and (as a last option) the use of personal protective equipment, as well as worker. However, even in occupations with a well-recognized risk of sensitization, such as work involving laboratory animals, implementation of and knowledge about preventive measures in the workplace has been suboptimal.

Secondary prevention includes early identification of workers with occupational exposure to asthma-causing agents by means of medical surveillance (periodic respiratory questionnaires with or without spirometry and immunologic tests) and further investigations to confirm diagnosis and then remove the person from further exposure. Such measures have been introduced in some companies for at-risk workers - for example, persons who work in bakeries; those who work with animals, detergents, diisocyanates, or complex platinum salts; and epoxy workers exposed to acid anhydrides. Studies suggest that such programs are beneficial, although the benefit is difficult to specify precisely because of the multicomponent nature of the programs. It has been suggested that the questionnaire component is likely to be most predictive among bakers but may be less reliable among respondents who believe that their answers might result in job loss.

Asthma symptoms and airway hyper-responsiveness persist in approximately 70% of patients with occupational asthma, even several years after removal from the offending environment. Outcomes are best when the diagnosis is established early, the exposure is stopped, and the asthma is not yet severe. Appropriate management after diagnosis, in addition to prevention of further exposure when possible, involves tertiary prevention with pharmacologic management that follows clinical-practice guidelines.

Recent systematic reviews indicate that complete and definitive avoidance of exposure to the causal agent remains the preferred approach to the management of immunologic occupational asthma. Although reduction of exposure to the agent can be considered an alternative to complete avoidance of exposure, the limited available evidence indicates that reduced exposure is less beneficial than exposure cessation.

Is asthma being overdiagnosed?

According to experts, more than a million people receiving treatment for asthma may have been misdiagnosed. National Institute for Health and Care Excellence (NICE) have stated that, almost a third of the 4.1m people treated for asthma in the UK did not show any 'clear evidence' of the incurable condition, which denotes that the patient may be receiving unnecessary treatment.

NICE has drafted new guidance, for asthma, for doctors in England to improve the accuracy of diagnoses which makes it clear that a clinical test should be carried out to diagnose asthma, as well as checking for signs and symptoms. Under proposed NICE guidance- GPs will have to carry out a battery of assessments to ensure they have an 'objective' diagnosis of asthma – including exhaled FeNO and bronchial challenge tests .

The new draft guidelines completely bypass the option to carry out a trial of therapy as means to diagnose asthma – currently advised by the recently updated gold-standard SIGN/BTS guidelines on diagnosis – and will see GPs required to get extra tests to confirm a diagnosis. These will include in some cases measurement of airways inflammation and hyper-reactivity – or 'twitchiness' – for which tests are currently not widely available, even in specialist services.

According to NICE, new guidelines on diagnosis and monitoring of asthma are needed because 'there is evidence that incorrect diagnosis is a significant problem'. Studies suggest up to 30% of people do not have clear evidence of asthma and while some may previously have suffered it, many patients will have been wrongly diagnosed as asthmatic, NICE advisers said.

The move was welcomed by GP experts in respiratory medicine although they cautioned that the guidelines would need significant investment to implement – irrespective of whether GPs are expected to perform the tests themselves in primary care, or to refer more patients to secondary care for investigations.

The draft guidelines cover both children and adults, and key recommendations for those aged over five years include the need to carry out 'objective' testing to diagnose asthma, including initial spirometry tests, follow-up bronchodilator reversibility (BDR) tests and exhaled FeNO tests.

Bronchial challenge tests are also recommended in some cases where there is still uncertainty over the diagnosis.

Any patients considered likely to have occupational asthma should be referred to a specialist straight away, while for children aged under five, GPs should treat symptoms based on their clinical judgement and only perform further tests once the child is considered old enough to take part – usually at around five years of age.

Asthma breakthrough: potential cause and corrective treatment are identified

A paper published in Science Translational Medicine reports that the root cause of asthma has been found and a potential treatment to reverse all symptoms has been proposed. Cardiff University researchers, working in collaboration with scientists at King's College London and the Mayo Clinic (USA), describe the previously unproven role of the calcium sensing receptor (CaSR) in causing asthma, a disease which affects 300 million people worldwide.

Crucially, the paper highlights the effectiveness of a class of drugs known as calcilytics in manipulating CaSR to reverse all symptoms associated with the condition. These symptoms include airway narrowing, airway twitchiness and inflammation - all of which contribute to increased breathing difficulty.

"Our findings are incredibly exciting," said the principal investigator, Professor Daniela Riccardi, from the School of Biosciences. "For the first time we have found a link airways inflammation, which can be caused by environmental triggers - such as allergens, cigarette smoke and car fumes – and airways twitchiness in allergic asthma.

Dr Samantha Walker, Director of Research and Policy at Asthma UK said: "This hugely exciting discovery enables us, for the first time, to tackle the underlying causes of asthma symptoms. Five per cent of people with asthma don't respond to current treatments so research breakthroughs could be life changing for hundreds of thousands of people.

According to Cardiff Professor Paul Kemp, who co-authored the study, the identification of CaSR in airway tissue means that the potential for treatment of other inflammatory lung diseases beyond asthma is immense. These include chronic obstructive pulmonary disease (COPD) and chronic bronchitis, for which currently there exists no cure. It is predicted that by 2020 these diseases will be the third biggest killers worldwide.Professor Riccardi and her collaborators are now seeking funding to determine the efficacy of calcilytic drugs in treating asthmas that are especially difficult to treat, particularly steroid-resistant and influenza-exacerbated asthma, and to test these drugs in patients with asthma.

Calcilytics were first developed for the treatment of osteoporosis around 15 years ago with the aim of strengthening deteriorating bone by targeting CaSR to induce the release of an anabolic hormone. Although clinically safe and well tolerated in people, calcilytics proved unsuccessful in treating osteoporosis.

"If we can prove that calcilytics are safe when administered directly to the lung in people, then in five years we could be in a position to treat patients and potentially stop asthma from happening in the first place," added Professor Riccardi.

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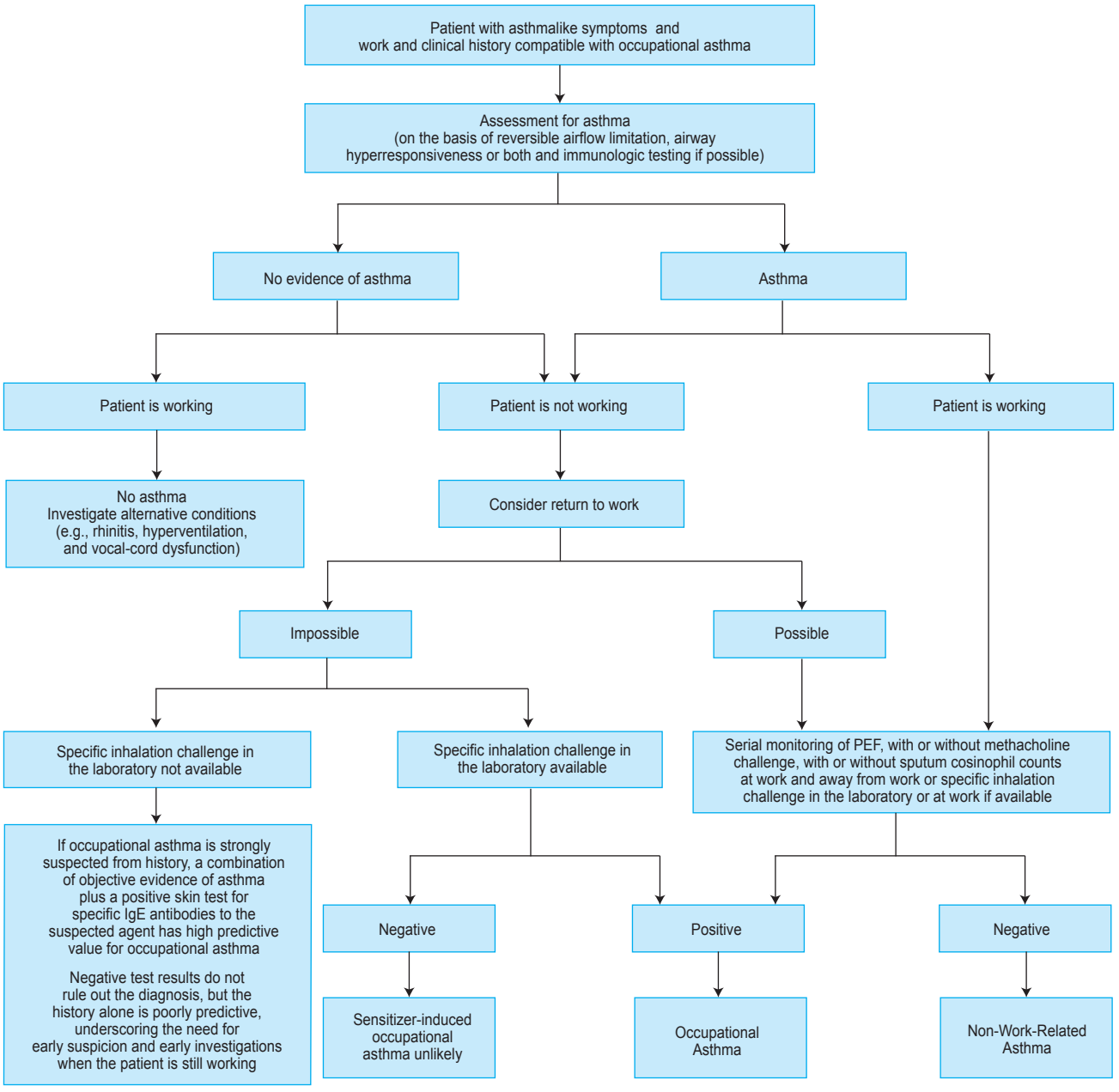
Figure 2. Algorithm for Evaluating an Adult with Asthma like Symptoms for Sensitizer-Induced Occupational Asthma



Immunotherapy has been tested for a few sensitizing agents with IgE-dependent reactions, mainly in health care workers who were allergic to latex but also in small numbers of workers who were allergic to cereal, sea squirt, and laboratory animals. Although immunotherapy can reduce cutaneous and respiratory symptoms, systemic reactions often occur. Whether asthma outcomes are altered in the long term remains to be determined, and further studies are needed before immunotherapy can be recommended. Improvement with the monoclonal anti-IgE antibody omalizumab has been reported in a few patients with occupational asthma who remained exposed to the causal agent, but it also requires further prospective studies.

Irritant-Induced Asthma: There is less information on the prevention of irritant-induced asthma than on the prevention of sensitizer-induced asthma, since the most straight forward cases of irritant-induced asthma are due to accidental exposure.

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Table 3. Prevention of Sensitizer-Induced Occupational Asthma.

Primary prevention
Avoid introducing predicted new sensitizing agents into the workplace (efficacy as primary prevention currently theoretical).
Avoid use of known sensitizing agents if safer alternatives are available.
Modify the physical or chemical form of known sensitizers to reduce risk of exposure (e.g., less volatile preparations, polymerized products and latex gloves with a low-protein and low-powder content).
Reduce exposure to work sensitizers by means of occupational hygiene measures (e.g., use of robotics, containment, ventilation and respirators).
Educate workers in the use of safe practices at work.
Monitor and control levels of exposure to workplace sensitizers.
Secondary prevention (early detection)
Institute medical-surveillance programs for workers at risk consisting of preplacement and periodic respiratory questionnaires, with spirometry and immunologic tests as indicated.
Ensure that health care providers have adequate knowledge of occupational asthma and consider it early in the evaluation of all adults with asthma symptoms, leading to early diagnosis and management of occupational asthma.
Educate workers about the risks of occupational asthma through workplace-programs, information provided by health care providers and public-education programs (e.g., from news media, lung associations and web-based programs).
Tertiary prevention (appropriate treatment)
Evaluate symptomatic workers early and obtain an accurate diagnosis.
Remove workers from further exposure to the implicated agent after a confirmed diagnosis, when possible.
Control other triggers and use pharmacologic measures if necessary.
Assist the patient with a workers' compensation claim when applicable, to limit the socioeconomic effects of the diagnosis.
Monitor the patient's asthma in future work locations to ensure safe placement.

Prevention should include occupational-hygiene measures that ensure the safety of workers in environments where there is the potential for accidental exposure to irritants. General measures include containment, good ventilation, worker education regarding safety practices, and, when other measures are not sufficient, use of fit-tested respiratory protective devices.

Conclusions

Occupational asthma is potentially preventable in most cases. Furthermore, an improved understanding of occupational asthma may enhance our knowledge about other types of asthma. To minimize the risk of long-term impairment from occupational asthma, health care practitioners should consider this diagnosis early in their evaluation of adults with symptoms of asthma.

Reference: Tarlo SM, Lemiere C. Occupational asthma. *N Engl J Med.* 2014;370(7):640–9. A comprehensive review on occupational asthma.

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Congratulations!!!

The Winners of Asthma Focus Quiz Competition

Vol. 11 No. 1

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Editorial Note

Dear Doctor,

We are happy to present you the 2nd issue of "Asthma Focus" Newsletter, 2015. In this issue we have concentrated 'Occupational asthma '. We hope you will enjoy reading the publication!

We appreciate your comments and queries.

Please participate in Quiz competition & win prizes.

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