

Canadian Thoracic Society Guidelines for occupational asthma

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OBJECTIVE: To provide broad guidelines and principles to help primary care physicians, occupational physicians, allergists and respirologists with the recognition, diagnosis and management of patients with occupational asthma (OA).

OPTIONS: These guidelines are mainly directed towards OA induced by a workplace sensitizing agent. However, irritant-induced asthma and workplace aggravation of underlying asthma are also addressed, and some consideration is given to other differential diagnoses.

OUTCOMES: To enable the assessing physician to investigate patients with possible OA appropriately and to provide guidelines for appropriate early referral when specialized investigations are required. To provide an understanding of the appropriate management strategies following objective diagnosis.

EVIDENCE: The key diagnostic and management recommendations were based on a critical review of the literature and by specialist consensus meetings.

VALUES: Evidence was categorized as follows. Level 1: Evidence from at least one randomized, controlled trial. Level 2: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytical studies, preferably from more than one centre, from multiple time series or from dramatic results

in uncontrolled experiments. Level 3: Evidence from the opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees. Evidence was further subdivided as follows: A. Good evidence to support a recommendation for use; B. Moderate evidence to support a recommendation for use; C. Poor evidence to support a recommendation for or against use; D. Moderate evidence to support a recommendation against use; E. Good evidence to support a recommendation against use.

BENEFITS, HARM AND COSTS: The medical and socioeconomic risks and benefits of an incorrect diagnosis of OA and of failure to diagnose true OA were considered in the recommendations.

VALIDATION: The document has been reviewed and endorsed by the Canadian Thoracic Society, the Canadian Society of Allergy and Clinical Immunology, and The College of Family Physicians of Canada.

CONCLUSIONS: There is good evidence for rapid investigation and objective categorization of presented symptoms into OA, aggravation of underlying asthma, unrelated asthma or other diagnoses. OA should be suspected in all adult onset asthmatics whose asthma begins or worsens while they are working. Investigations should be directed to an objective assessment of asthma and then to an assessment of the work relationship, using a combination of investigations as feasible, which may include immunological tests, pulmonary function assessed during work periods and away from work, and specific challenge tests. Early specialist referral is recom-

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mended for diagnosis. Management strategies include general asthma management in addition to measures to avoid further exposure to a relevant workplace sensitizer. Compensation issues and other workers at risk of developing OA also need to be considered when the diagnosis is made.

Key Words: *Asthma, Guidelines, Occupational asthma, Workplace*

Directives de la Société canadienne de thoracologie pour l'asthme professionnel

OBJECTIF : Offrir des directives et des principes généraux pour aider les médecins de premier recours, les médecins du travail, les allergistes et les pneumologues à reconnaître, diagnostiquer et traiter les patients souffrant d'asthme professionnel (AP).

OPTIONS : Ces directives concernent principalement l'asthme professionnel provoqué par un agent sensibilisant dans le milieu de travail. Toutefois, l'asthme provoqué par les irritants et l'aggravation au travail d'un asthme préexistant sont également abordés et on mentionne en outre d'autres diagnostics différentiels.

VISÉES : Permettre aux médecins d'examiner les patients présumés atteints d'un asthme professionnel de façon appropriée et fournir des directives quant aux demandes de consultation en temps opportun lorsque des examens plus approfondis sont nécessaires. Expliquer les stratégies thérapeutiques appropriées, une fois le diagnostic objectif posé.

PREUVES : Les recommandations diagnostiques et thérapeutiques clés se fondent sur l'examen critique de la littérature et sur le consensus auquel en sont venus les spécialistes lors des réunions.

VALEURS : Le degré de preuves a été catégorisé comme suit : degré 1 : preuves tirées d'au moins un essai contrôlé randomisé; degré 2 : preuves tirées d'au moins un essai clinique bien structuré, sans randomisation, à partir d'études de cohortes ou d'études analytiques avec cas/témoins, préféablement de plus d'un centre sur de multiples périodes ou à partir de résultats probants lors d'expériences non contrôlées; degré 3 : preuves fournies par des

sommités respectées sur la base de l'expérience clinique, des études descriptives ou des rapports de comités d'experts. Les preuves ont de plus été subdivisées de la façon suivante : a) bon degré de preuves pour appuyer une recommandation d'emploi; b) degré modéré de preuves pour appuyer une recommandation d'emploi; c) faible degré de preuves pour appuyer une recommandation pour ou contre l'emploi; d) degré de preuves modéré à l'appui d'une recommandation contre l'emploi; e) bon degré de preuves pour appuyer une recommandation contre l'emploi.

AVANTAGES, PRÉJUDICES ET COÛTS : Les risques et les avantages médicaux et socio-économiques d'un diagnostic erroné d'asthme professionnel ou d'un asthme professionnel non diagnostiqué sont entrés en ligne de compte dans ces recommandations.

VALIDATION : Le document a été passé en revue et appuyé par la Société canadienne de thoracologie, la Société canadienne d'allergie et d'immunologie clinique et le Collège des médecins de famille du Canada.

CONCLUSIONS : Sur la base des preuves actuelles, on préconise un diagnostic rapide et la catégorisation objective des symptômes, selon qu'il s'agit d'un asthme professionnel, de l'aggravation d'un asthme préexistant, d'un asthme non professionnel ou d'autres catégories. L'asthme professionnel doit éveiller les soupçons chez tous les asthmatiques dont la maladie se déclenche à l'âge adulte, dont l'asthme commence ou s'aggrave lorsqu'ils sont au travail. Les examens doivent être axés sur une évaluation objective de l'asthme, puis sur une évaluation du rapport entre les symptômes et le travail effectuée au moyen de tests divers, selon leur accessibilité. Parmi ces tests, on retrouve notamment les tests immunologiques, les tests de fonction pulmonaire durant le travail et à l'extérieur du travail et des tests de provocation spécifiques. On recommande aux médecins d'adresser leurs patients en consultation sans délai pour confirmer le diagnostic. Les stratégies thérapeutiques sont, entre autres, le traitement général de l'asthme, en plus de mesures visant l'évitement d'autres expositions à un agent sensibilisant au travail en particulier. Les problèmes de compensation et l'exposition des autres travailleurs au risque de l'asthme professionnel doivent également être envisagés lors du diagnostic.

GOALS AND OBJECTIVES

The Canadian Thoracic Society Subcommittee on Occupational Asthma was reassembled in 1996 to develop guidelines on the diagnosis and management of occupational asthma (OA). A previous statement by the subcommittee on the diagnosis and management of occupational asthma was published in 1989 (1), and a need was recognized for an updated document. Most primary and secondary care physicians see only a few such patients. Nevertheless, the medical, social and economic consequences of this condition mandate that an early, accurate diagnosis be reached. This document is directed predominantly at the family doctor, internist, general respirologist and occupational physician who see patients with occupational asthma. The guidelines were developed according to the Canadian Medical Association's Guidelines for Canadian Clinical Practice Guidelines (2). Consultants from the specialties of respiratory and occupational medicine were invited to become members of the Canadian Thoracic Society Subcommittee on Occupational Asthma. They were asked to review the previous statement on occupational asthma (1), and to update and modify this statement in light of available peer reviewed published studies in this area from 1988 to 1996 – as listed in a MEDLINE

search for occupational asthma – and consensus from committee discussions. This document has been divided into consensus statements, followed by a review of the rationale for the statements. A series of recommendations follow with an indication of the level of evidence for the recommendations.

The definition of the levels of evidence used to grade the recommendations in these guidelines is taken from the 1996 *Report on the working groups for the Canadian Asthma Consensus Conference* (3) (Table 1).

Most of the current document will address the new onset of asthma caused by the workplace environment, but some consideration will also be given to other effects of the workplace on asthma, particularly workplace aggravation of underlying asthma.

Agents in the workplace can cause the new onset of asthma but can also cause aggravation of underlying asthma.

OA describes asthma caused by exposure to an agent found in the workplace. It is usually new onset asthma but can occasionally occur in people with pre-existing asthma. It can be due to an allergic type of response to an agent of high or low molecular weight, either through production of immu-

TABLE 1
Strength and quality of evidence summary

Categories for quality of evidence on which recommendations are made
Level 1: Evidence from at least one randomized controlled trial
Level 2: Evidence from at least one well designed clinical trial without randomization, from cohort or case-control analytical studies, preferably from more than one centre, from multiple time series or from dramatic results in uncontrolled experiments
Level 3: Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
Category of strength for each recommendation
A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation for or against use
D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

Data adapted from reference 3

noglobulin (Ig) E antibodies or by unknown, presumed immunological mechanisms (Table 2) (4). Alternatively, and less commonly, asthma can be induced by a high level respiratory irritant exposure at work. However, in an occupational lung disease clinic, work-related effects on asthma are also commonly seen because of aggravation of pre-existing asthma by the workplace exposure, usually on a short term basis (5). One of the hallmarks of asthma is hyper-responsiveness of the airways to respiratory irritants (eg, dusts, smoke, fumes and sprays), cold or dry air, and exercise. Where these triggers are present in the workplace, the asthmatic worker is likely to note that his or her symptoms worsen. Irritant exposure is more likely to exacerbate asthma symptoms if general asthma control has been suboptimal or if asthma is relatively severe (3). This exacerbation of asthma needs to be distinguished from OA because the management differs and most patients with aggravation of underlying asthma can continue to work with appropriate asthma management and often with relatively small workplace modifications. In the experience of this committee, irritant aggravation of underlying asthma is the most common differential diagnosis of OA and is a common source of misunderstanding for both patients and physicians.

OA is relatively common among working adults with asthma.

Asthma is a common condition affecting about 5% to 10% of the population (6). When asthma is caused by exposure to an agent specific to a workplace and not to stimuli encountered outside the workplace, it is termed OA (7). In most circumstances, the nature of the responsible agent can be identified. Recent studies estimate that 3% to 7% of new onset adult asthma may be caused by the workplace (8-10), with higher estimates given in a disability survey (11).

Diagnosis of OA should be confirmed as soon as possible and is essential before advising a patient to leave work.

Proper management of a patient in whom OA is suspected depends on the initial establishment of a definitive diagnosis.

TABLE 2
Common agents that cause occupational asthma with latency and workers who are at risk

Agents	Workers at risk
High molecular weight agents	
Cereals	Bakers, millers
Animal-derived allergens	Animal handlers
Enzymes	Detergent users, pharmaceutical workers, bakers
Gums	Carpet makers, pharmaceutical workers
Latex	Health professionals
Seafoods	Seafood processors
Low molecular weight agents	
Isocyanates	Spray painters, insulation installers, manufacturers of plastics, rubbers, foam
Wood dusts	Forest workers, carpenters, cabinetmakers
Anhydrides	Users of plastics, epoxy resins
Amines	Shellac and lacquer handlers, solderers
Fluxes	Electronic workers
Chloramine-T	Janitors, cleaners
Dyes	Textile workers
Persulphate	Hairdressers
Formaldehyde, glutaraldehyde	Hospital staff
Acrylate	Adhesives handlers
Drugs	Pharmaceutical workers, health professionals
Metals	Solderers, refiners

Reproduced with permission from reference 4. Further details of occupational asthma causes can be obtained from the American Academy of Allergy database on causes of occupational asthma (a diskette is available)

In addition to medical management, subsequent management of patients with OA may include removal from work, resulting in significant socioeconomic consequences, and compensation or medicolegal issues. Therefore, an accurate diagnosis is essential to prevent unnecessary lifestyle changes for the patient, especially before advising a patient to leave work, and to allow clear and confident medicolegal opinions to be given. In addition, when the patient truly has OA induced by a workplace ‘sensitizer’, as defined below, the outcome of the asthma is better with early removal from exposure to the sensitizers. Therefore, the diagnosis should be established as soon as possible.

Most OA is due to a specific workplace sensitizer.

In most cases of OA, the responsible agent can be identified. The most common type of OA is that caused by sensitization to a high or low molecular weight agent that causes asthma after a latency period of exposure, which can range from weeks to years (12). Following sensitization, re-exposure, even to low levels of that agent, may cause an asthmatic response. For most high molecular weight agents, the

mechanism of immunological sensitization is identified and is IgE-mediated, eg, latex proteins (as in health care workers), wheat or other flour (as in bakers), enzymes (as in bakers [fungal or cereal amylase], some laboratory workers and detergent workers) and animal allergens (as in some laboratory workers). Low molecular weight chemicals can also cause OA by sensitization through an IgE-mediated response (eg, complex platinum salts or epoxy resins) (Table 2). However, for most low molecular weight agents such as diisocyanates, plicatic acid (in red or white cedar dust), cyanoacrylates, methacrylates (in glues) or colophony (in electronic soldering flux), the mechanism of sensitization remains unknown, although the presence of a latency period points to an immunological mechanism. The workplace exposure levels leading to sensitization are generally levels that are not considered to cause respiratory irritation and are within allowable industrial standards. Sensitization to a workplace agent accounts for over 90% of all OA in workers' compensation board claimants (13).

High level acute respiratory irritant exposure at work less commonly causes asthma.

Less commonly (accounting for about 6% of cases [13]), OA can be caused by a very high level irritant exposure at work (irritant-induced asthma). When related to a single very high level (a level well above allowable standards) of a respiratory irritant agent, this is termed reactive airways dysfunction syndrome (RADS) (14). The term 'irritant-induced asthma' has been used to describe this effect resulting from one or more high level exposures. Such an exposure is usually the result of a spill or other accident leading to high levels of an agent that is known to be a respiratory irritant, eg, acids, chlorine, ammonia or high level diisocyanates. This can result in an asthma syndrome, starting within 24 h of exposure that can persist for months or years. Unlike OA due to a sensitizer, the asthma is induced without the need for a latent or sensitizing period of exposure (ie, it can occur on the first day of high level exposure). Re-exposure of such patients to low levels of that agent will not generally trigger their asthma, although moderate or high levels of exposure to any respiratory irritant could aggravate their symptoms as in patients with nonwork-induced asthma. The long term functional consequences of irritant-induced asthma may differ from OA due to a sensitizing mechanism. However, limited data are available to assess this.

A few chemicals such as isocyanates with the potential of causing OA through sensitization can also cause OA after high level irritant exposure. In some cases, an irritant exposure to a high level of such a chemical causes concurrent sensitization in addition to inducing irritant OA so that subsequent low level exposures to that agent would trigger asthma.

Although the initial description of irritant-induced asthma (RADS) (14) placed the onset of asthma within 24 h of a single very high irritant exposure, subsequent reports (15-18) have described and reviewed the evidence for the onset of irritant-induced asthma after more than one high level irri-

tant exposure, as with workers in pulp and paper mills exposed intermittently to high levels of chlorine. However, for an individual patient, it is difficult to distinguish this from the coincidental onset of nonwork-induced asthma. It remains a controversial diagnosis unless there is a clear relation between at least one high exposure and the onset of asthma within 24 h, in the absence of previous lung disease.

Asthma starting at work is not always OA.

OA due to a sensitizer or due to an irritant needs to be distinguished from the coincidental onset of asthma unrelated to the workplace. Asthma is a common condition, affecting at least 5% of the population (6), and is most often causally unrelated to work. It has been estimated that about 5% of isocyanate or red cedar workers, or latex glove manufacturers become sensitized and develop OA. However, the development of asthma during employment with exposure to a known respiratory sensitizer, although raising the suspicion of OA, does not prove the diagnosis of OA. Other causes of asthma-like symptoms that may or may not be work-related should also be included in the differential diagnosis, eg, bronchitis or other pulmonary disease, hyperventilation, vocal cord dysfunction, cough from a postnasal drip and rhinitis, and cardiac disease. These can coexist with asthma or can occur separately. They may be distinguished by a careful history and should be especially considered when objective tests for asthma (pulmonary function tests, including methacholine or histamine challenge tests carried out shortly after leaving work) are normal.

A diagnosis of OA should be considered in all working-age asthmatics. However, history alone is not sufficient for the diagnosis.

A history of asthma beginning during a working lifetime should lead to consideration of OA. Suspicion is increased if the patient describes worsening of symptoms on working days compared with weekends or holidays off work. He or she may describe worsening within minutes of going into work (immediate asthmatic responses) or after several hours, and sometimes occurring in the evening or night after leaving work (late asthmatic responses). The patient may also exhibit both early and late responses (dual asthmatic responses). Isolated late responses are more typical of sensitization to isocyanates and red cedar dust, but any sensitizer can produce immediate or dual responses. A patient's history has been found to have high sensitivity (96%) but low specificity (about 25%) for the diagnosis of OA (for example, an irritant trigger at work typically also exacerbates symptoms of nonwork-related asthma almost immediately on exposure) (19). Thus, further objective investigations are needed when such a history is obtained to confirm or exclude OA or some other work relationship to asthma. Workplace exposure should be assessed in the history, and the relevant Material Safety Data Sheets (for all work agents that the patient may be directly or indirectly exposed to at work) should be obtained by the patient or from the employer for the physician to review. However, one must be mindful that the absence of a known

respiratory sensitizer does not exclude OA because new causes of OA are described each year.

First, demonstrate the presence of asthma objectively. Then, use objective tests to assess the relationship with work.

The assessment of suspected OA has been well reviewed in a recent consensus statement from the American College of Chest Physicians (20). The first step following the history and physical examination is to confirm objectively that the patient does indeed have asthma. Because exposure to the sensitizing agent may induce a short term increase in airway reactivity, particularly early in the course of OA, it is important that spirometry pre- and postbronchodilator be assessed within 24 h of typical workplace exposure or at a time when symptoms are present. If spirometry is normal, then a histamine or methacholine challenge should be performed, also within 24 h of typical workplace symptoms, to determine the presence or absence of airway hyper-responsiveness, a hallmark feature of asthma. Although a few cases have been described of confirmed OA with normal airway responsiveness after a few days at work or after a positive specific challenge test outside of the workplace (21,22), these reports are very uncommon. Thus, for practical purposes, a normal methacholine response in a *symptomatic* patient who is still working rules out OA. In that event, another diagnosis should be considered, eg, bronchitis, hyperventilation, vocal cord dysfunction or postnasal drip. However, in a patient who has been away from the work exposure that was associated with symptoms, and in whom symptoms have cleared, a normal methacholine test does not rule out OA.

Use objective tests to assess the work relationship of asthma.

If the diagnosis of asthma is objectively confirmed by pulmonary function tests, the next step is to assess objectively the relationship of asthma to work. However, as noted above, if the patient gives a history of experiencing symptoms of asthma at work and the patient is initially assessed at a time when symptoms have cleared after he or she has been off work, the absence of objectively demonstrable asthma does not exclude work-related asthma. The relationship of previous symptoms to work still needs to be assessed.

Tests used to assess the relationship of asthma to the workplace consist of the following: a) immunological tests, eg, skin prick tests or serum radio-allergosorbent (RAST) or enzyme-linked allergosorbent testing (ELISA), to identify specific IgE antibodies to a workplace allergen; b) serial self-recording by the patient of peak expiratory flow readings or spirometry over the course of several weeks at work and off work; c) serial histamine or methacholine challenges within 24 h of typical work exposure and after several weeks off work; and d) specific occupational laboratory challenge tests. Each of those investigations has advantages and disadvantages.

a) When skin tests with workplace agents are feasible, a positive response increases suspicion of OA.

Skin prick tests can be performed for high weight molecu-



Figure 1) Positive skin prick test to pectin in a maker of jam with occupational asthma. Reproduced with permission from reference 22

lar allergens (eg, animal or plant extracts) or for complex platinum salts. However, few occupational allergen extracts are commercially available for skin testing or in vitro immunological tests; extracts are not standardized, and those that are available may not be good antigenic extracts for the suspected causative agent. The testing of patients with nonstandardized solutions can only be interpreted as positive when testing of control subjects with the same solutions is negative and the results of skin testing with the diluent are negative in both patients and controls. A negative response with an inadequate extract does not exclude immunological sensitization. RAST or ELISA can be useful for a few low molecular weight sensitizers such as epoxy resins, but neither investigation is useful for the most common sensitizers, isocyanates and plicatic acid. The finding of a true positive skin test (Figure 1) (23), or a positive RAST or ELISA, indicates the presence of specific IgE antibodies to the allergen, but does not by itself indicate a symptomatic response to that allergen. If the patient who has objectively confirmed asthma is exposed to that allergen at work and gives a consistent history of OA, it is likely that the patient has OA related to that allergen (24). The degree of airway responsiveness to an allergen is related to a combination of the degree of airway hyper-responsiveness to histamine and the degree of skin test re-

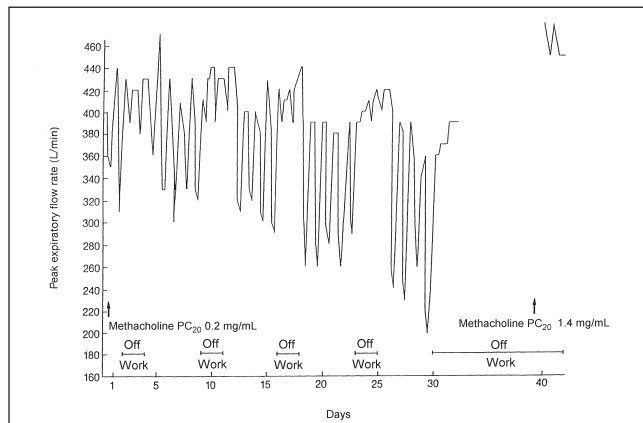


Figure 2) Peak flow results and methacholine concentration provoking a 20% fall in forced expiratory volume in 1 s (PC₂₀) in a surgical glove inspector with occupational asthma from latex sensitization. Reproduced with permission from reference 29

sponsiveness to that allergen (25). Nevertheless, when possible, more direct additional objective evidence of the work relationship should be obtained as detailed below.

b) Peak expiratory flow recordings at work and off work require careful patient instruction and should be initiated early in investigation.

Often the suspected agent in the workplace cannot be used for skin or in vitro tests of IgE antibodies, and even when the tests could be used, more direct assessment of the work relationship to asthma is needed. If the patient is still working when assessed or if he or she is off work but can return to the workplace, serial monitoring of peak expiratory flows or spirometry, in addition to serial histamine or methacholine challenges, is indicated.

The patient should be carefully instructed in the correct use of the peak expiratory flow meter or portable spirometer, and be asked to perform readings at least four times a day during several working weeks and during a period of weeks off work (if possible for four weeks, but at least for two weeks). On each occasion, the patient should perform at least three expiratory efforts, and these efforts should be recorded, either by electronic equipment (this can register the best effort) or by the patient on a written diary record. Electronic peak expiratory flow meters or spirometers are preferable if available because they provide more objective evidence and allow better assessment of compliance. However, in most centres, inexpensive nonelectronic peak expiratory flow meters are more available for patients to borrow or buy, and peak expiratory flow rate results using these meters have been shown to correlate well with other, more objective tests for OA in previous studies (26-29).

Patients should also keep a diary record of symptoms, medication use and work activities. They should be asked to record additional peak expiratory flow measures before any use of inhaled bronchodilators and to note on the diary whether recordings are made at home or at work (30). Regularly used medications such as inhaled corticosteroids should, if possible, be maintained at a steady dose during the

assessment period to avoid false positive or negative peak expiratory flow results due to medication changes. Peak expiratory flow recordings may be made interpreted by visual inspection of a plotted graph of recordings at home and at work (31) (Figure 2) (32). Worsening of peak expiratory flow rates at work versus those on days off work suggests OA or work-related aggravation of asthma. Objective criteria for peak expiratory flow interpretation have not been universally accepted. Diurnal variability of at least 20% is suggestive of asthma, and if such variability occurs relatively more often on working days than days off work, this is suggestive of an occupational effect (26,27).

Peak expiratory flow recordings are effort-dependent and patient compliance may be poor.

There are limitations to the use of peak expiratory flow monitoring. It is effort-dependent and requires good patient compliance; results can be falsified (33,34), and peak flows can underestimate changes in airway calibre in comparison with measures of forced expiratory volume in 1 s (FEV₁) (35). Positive peak flow recordings only help to establish a work relationship to asthma; they do not identify the causative agent. In addition, the recordings require a patient to be off work for a period of time to obtain results for comparison with those readings taken when the patient is at work. The recordings may be falsely negative if the patient is receiving enough medication to suppress work-related airflow changes or if the patient is not exposed to the relevant agent during the monitoring time. The recordings are not helpful if the patient has already left work and cannot return to the workplace. Therefore, the committee recommends additional investigations to confirm or exclude OA. It particularly recommends performance of methacholine challenge within 24 h of work exposure and after a period away from work, concurrent with the period of peak flow monitoring. The results of peak flow monitoring support or exclude OA only when they are concordant with results of methacholine monitoring. When results are discordant, further tests are needed. This consists of specific challenges either at work or in the laboratory with suspected workplace agents.

c) Serial histamine or methacholine challenges after a work day and holiday can provide an objective supplementation to peak expiratory flow monitoring.

For patients who are monitoring peak expiratory flows at home and work, it is helpful to obtain further objective information if possible. A methacholine or histamine challenge can be performed towards the end of a working week (ie, while working) and at the end of two to four weeks away from work, eg, at the end of a holiday period, during the same period as serial peak expiratory flow monitoring. The finding of a significant improvement in airway responsiveness away from work (in most laboratories this would be a three- to fourfold increase in the concentration of histamine or methacholine that produces a 20% fall in FEV₁ [36]) or significant deterioration upon return to work is highly supportive of OA. Other factors that may alter responsiveness include changes in nonoccupational allergen exposure, viral infections, medications such as bronchodilators taken just before the test and

changes in corticosteroid dosage. All of these factors need to be accounted for in the interpretation of results. The baseline spirometry at the onset of each test must also be comparable; the results of FEV₁ measurements before each challenge should be within 10% of each other.

The finding of peak expiratory flow worsening at work but without accompanying changes in airway responsiveness may support the diagnosis of work-related aggravation of asthma, if there is a known respiratory irritant. But it may also reflect OA due to a sensitizer when the assessment is performed without a sufficient period off work. If a workplace sensitizer has been identified, but tests cannot be performed to detect IgE antibodies, a longer period of assessment off work may be needed to rule out OA. Specific laboratory challenge could be performed with the suspected workplace sensitizer more easily in some centres, obviating the additional waiting time.

Early referral for investigation of OA while the patient is still working greatly facilitates an accurate diagnosis.

It is especially important that the patient not be advised to quit his or her job until adequate investigations have been performed. Early referral and rapid access to a physician able to arrange investigations is needed because the diagnosis is often very difficult to establish in patients who have left work and cannot or will not return.

d) Specific laboratory challenge tests require specialized facilities. They can provide a definitive diagnosis of occupational asthma and its cause but are not necessary in all patients, especially if workplace studies, ie, sections b) and c), are conclusive.

Specific laboratory exposure testing with the suspected workplace sensitizer provides the most definite confirmation of OA. Since the early descriptions of these tests (37), specific laboratory exposure testing has proven invaluable in defining the wide range of agents causing OA and in elucidating its pathogenesis. Methods have been developed by which such tests may be safely performed, using sophisticated delivery systems and careful monitoring (38,39). However, specialized facilities are required, and the tests are time consuming and expensive. If a facility where such tests can be safely performed is readily available, they may be used relatively early in the diagnostic process and may enable the diagnosis to be made faster than diagnosis by peak expiratory flow monitoring and methacholine challenges during periods at work and away from work. In most areas of Canada, such facilities are not readily available, and referral for challenge is made only if the diagnosis cannot be made by other tests.

Specific laboratory challenges must be carefully controlled to provide exposure to an appropriate level of the sensitizer, with appropriate pulmonary function monitoring for at least 6 h after exposure on an active and a control exposure day (Figure 3) (40). If the suspected agent has not been previously used for challenge testing in the particular laboratory, considerable time and resources are often needed to establish appropriate exposure conditions. The sensitivity of the test may be improved by performing histamine or methacholine

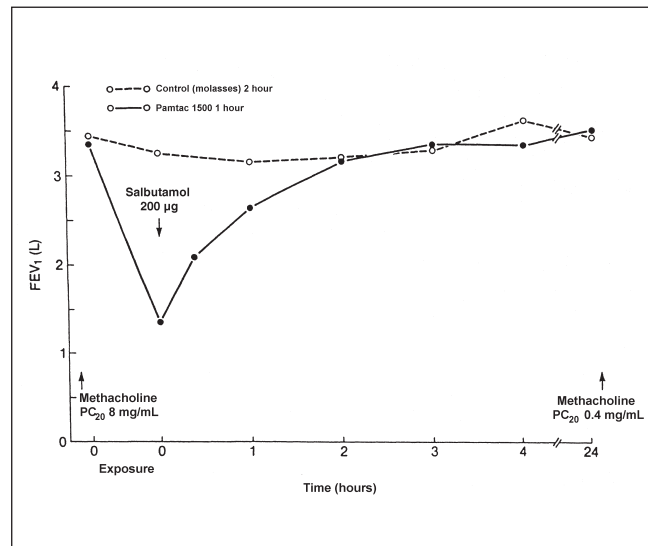


Figure 3) Occupational agent laboratory challenge results in a rubber tire worker sensitized to a pine product contained in a glue. Reproduced with permission from reference 33

tests on the days before and after the specific work agent exposures (41).

As with other investigations, false positive and false negative occupational challenge responses do occur. False positive responses may occur in unstable asthma, coincidental exposure to triggering factors or exposure to irritant levels of the exposure agent. False negative responses can occur from exposure to the wrong workplace agent, inadequate exposure levels or exposure duration, loss of specific reactivity after a period away from exposure, suppression of the response by medications, or failure to assess changes in methacholine responsiveness pre- and postchallenge. Thus, specific challenge tests should only be performed in specialized centres that are able to control such confounding factors. Expansion of such facilities may prove cost effective in areas with a high prevalence of suspected OA because a well controlled challenge may obviate the need for up to four weeks paid leave off work that can be required for peak flow monitoring.

All individual investigations for OA can be falsely positive or negative. The investigation of OA is a stepwise procedure that includes a combination of tests for each patient. This approach is most likely to lead to a definitive diagnosis.

Diagnosis of irritant-induced asthma (RADS) is based on history, documentation of exposure and objective tests of asthma.

The diagnosis of OA due to a high level irritant generally cannot be confirmed by objective tests, but depends on objective demonstration of asthma, a history of onset within hours of exposure at work, a duration of symptoms of at least three months and the absence of preceding lung disease (13). Documented visits to an emergency or first-aid department for acute symptoms can add support to the history of an acute respiratory event.

Aggravation of underlying asthma is diagnosed from history, evidence of a workplace asthma trigger and documented pulmonary function test changes.

Aggravation of underlying asthma may be diagnosed in patients with pre-existing asthma, objectively documented, who have exposure to recognized workplace asthma triggers and have transient worsening of asthma at work (usually lasting from a few hours to a few weeks) as demonstrated by serial peak flows or spirometry. Typically, there is no worsening of responsiveness to methacholine or histamine compared with results before the exposure.

MANAGEMENT OF OA

General asthma management

During investigations, control asthma as for non-OA.

During the period of diagnostic investigations and following diagnosis, the patient should have appropriate treatment for asthma, consistent with recent guidelines (3). Nonoccupational, nonallergic triggering factors for asthma and non-occupational allergen effects should be identified from history and skin testing. Appropriate environmental control measures should be instituted, eg, cessation of smoking, and control of dust mites or animal exposure, if relevant. Medication use should include regular anti-inflammatory medication such as inhaled steroids, and inhaled bronchodilators as needed. The patient should be educated about his or her asthma, warning signs of exacerbations and appropriate environmental control measures and medication use. If the patient is undergoing diagnostic investigations while still working, it is particularly important that he or she understand the warning signs of asthma and have an action plan to contact his or her physician and expedite laboratory pulmonary function testing before a severe asthma exacerbation develops. If asthma is clearly and objectively worse at work, the patient should be moved from the work area and their asthma objectively assessed while away from the suspected workplace sensitizer to document any improvement.

Social issues, retraining and compensation issues

A workers' compensation claim should be initiated for workers who have coverage. The timing of initiation of a claim will depend on the individual worker's circumstances.

The diagnosis of OA has large social and economic implications for the worker, his or her family, the employer and government agencies (42); as an example, the cost of one accepted OA claim in Quebec has been estimated to be \$50,000 (43).

If the diagnosis of OA has been made or is strongly suspected, a compensation claim should be initiated if the patient is covered by a workers' compensation system. In many jurisdictions, the physician has a duty to report occupational disease to the relevant workers' compensation system and occupational health and safety agency. The availability of as much objective documentation as possible in relation to the diagnosis will assist compensation or medicolegal claims. It is particularly useful to have clear paper copies of all pulmo-

nary function data and to ensure that the laboratories producing these data have conformed to appropriate standards for the procedures (44,45). In some areas, workplace aggravation of asthma may also be accepted for compensation.

In a survey of subjects with OA carried out in Quebec, it was shown that sensitizer-induced OA causes a small but significant impact on the quality of life (46) compared with non-OA. In particular, when patients have to leave work to avoid continuing exposure to a sensitizer the loss of earning may not be fully recovered (42,48).

Work implications and prognosis

Patients with confirmed sensitizer-induced OA must be removed from exposure to the sensitizer to obtain the best outcome of their asthma.

The distinction between sensitizer-induced OA and irritant-induced OA is important because the management differs. Those with sensitizer-induced OA should not be exposed to the workplace sensitizer, even at low levels. In contrast, those with irritant-induced asthma and/or underlying asthma can continue work in the same building but should be transferred to areas where accidental exposure to high levels of irritants is unlikely, or where industrial hygiene measures have been applied to reduce risks of a similar exposure. The patient with confirmed OA from a sensitizer should be *completely* removed from future exposure to that agent to have the best chance of improvement or clearing of his or her asthma (49). Occasionally, this may be achieved by a change in the process at work or by enclosing the process, improving ventilation or providing the workers with an appropriate respirator for short term exposures. Long term respirator use has not been shown to be effective in management of sensitizer-induced OA because even minute exposures can trigger asthma. Most often, therefore, the worker has to move to a completely different area of the plant or change to a different workplace or occupation. The patient may be eligible to receive vocational rehabilitation or retraining through their compensation coverage and may require significant psychosocial support during this period of change.

Early diagnosis and removal from exposure lead to the best outcome from sensitizer-induced OA.

Follow-up studies have shown that a majority of patients with OA failed to recover completely even when assessed several years after cessation of exposure to the causative agent (49). The best prognosis is obtained by early diagnosis, early removal from further exposure to the sensitizer, and in patients with milder asthma at the time of diagnosis (11,50). In a follow-up study of OA in Ontario (13), 19% of patients had clearing of asthma and 47% had improvement at a mean follow-up time of 1.9 years. Follow-up assessments for compensation purposes should again use objective pulmonary function criteria (51).

Vocational rehabilitation should be initiated for patients who have to change their job.

Vocational rehabilitation should be given to the patients who are not immediately relocated to a safe workplace envi-

TABLE 3
Steps in the diagnosis of occupational asthma

1. Suspect in any working adult onset asthmatic	
2. History	<ul style="list-style-type: none"> • Improvement weekends or holidays • Exposure history • Review of Material Safety Data Sheets
3. Confirm asthma	<ul style="list-style-type: none"> • History and physical examination • Spirometry pre- and postbronchodilator • +/- airway responsiveness by histamine or methacholine challenge
4. If history suggests a possible sensitizer-induced occupational asthma	<ul style="list-style-type: none"> • Assess the work relationship by serial peak flow or spirometry monitoring – working weeks and two to four weeks off work, methacholine or histamine challenges at end of work week and after several weeks off work, and skin tests with work allergen if possible, with or without specific laboratory exposure challenge

TABLE 4
Management of occupational asthma

1. Treat the asthma	<ul style="list-style-type: none"> • Control of nonoccupational triggers • Asthma medications • Patient education
2. Work exposure	<ul style="list-style-type: none"> • For sensitizer-induced occupational asthma, avoid any further exposure by workplace modifications or moving patient. If this is not possible then reduce exposure to as low as possible • For irritant-induced occupational asthma protect against further high level exposure
3. Assist patient in relevant compensation claim and rehabilitation	
4. Consider co-workers	<ul style="list-style-type: none"> • Notify public health and/or company
5. Monitor patient's course objectively	

ronment. There is a need for active communication, with the patient's informed consent, between the treating physician and the workplace and/or compensation board to ensure the best chance for return to full employment in safe conditions. The relevant sensitizer and any cross-reacting sensitizers must be completely avoided. In addition, if the patient has remaining nonspecific airway hyper-responsiveness, even with appropriate asthma therapy, restrictions may need to be placed on environmental exposure to nonspecific asthma triggers, such as cold air, fumes and dusts, and patients may have some exercise limitation. Often the patient has a fear of returning to an industrial setting, and patient education is integral to the process. Close monitoring of the patient's asthma in a new work environment and appropriate adjustment in exposure or medications is also necessary.

In view of the prognostic implications and the socio-economic consequences of the diagnosis, it is extremely important to make an accurate, early diagnosis.

Patients with RADS or irritant-induced asthma can usually continue to work at the same job.

In contrast to patients with OA from a sensitizer, those with OA induced by a nonsensitizing high level irritant can generally continue the same work, if provisions are made to reduce the risk of a similar accidental exposure and with appropriate management of their asthma. However, if the initial irritant exposure was to high level isocyanates or other known sensitizers with irritant properties, the patient should have his or her asthma carefully monitored to ensure that the exposure did not also result in sensitization.

Patients with aggravation of underlying asthma may need some exposure modification at work and/or adjustment in their medications.

Patients with coincidental asthma that is aggravated by workplace dusts, fumes or sprays may also often continue to

work with the use of appropriate asthma medications and a reduction in exposure by improved ventilation, respirator use or a move to an area of the plant with less irritant exposure. Patients who have very severe asthma may need to change their workplace to a much cleaner environment or claim disability insurance.

Consideration of other workers

A diagnosis of OA is a warning that others in the same workplace may have OA or may be at increased risk.

The patient with OA should be considered to represent a 'sentinel event' (52) in the workplace. Consideration should be given to the possibility of OA in other exposed workers and measures should be taken where possible to reduce this risk by changes in work process, containment or ventilation improvements. Medical screening of co-workers may be coordinated by a plant physician or public health agency, often in conjunction with an occupational hygienist who may recommend appropriate workplace changes. The physician diagnosing a patient with OA, therefore, needs to know the appropriate local steps to take to initiate this process, through the company (with the patient's consent) and /or through a public health agency, such as the provincial ministry of labour.

Surveillance measures

Occupational surveillance in relatively high risk occupations may lead to earlier detection and improved outcome from OA.

Workers in occupations or exposures that carry a significant risk of OA should be considered for asthma surveillance. The goal is early detection of workers with OA in order to prevent morbidity and disability. Medical surveillance does not replace appropriate interventions in the work process to prevent sensitization but is useful as an adjunct. Such pro-

grams may be organized by a company physician. For example, in some detergent industries, workers with exposure to enzymes undergo periodic prick skin tests with the enzyme and complete a questionnaire to allow early detection of allergic symptoms and/or skin sensitization that might then lead to a move in job area. Development of positive skin tests to a workplace allergen also indicates a need to reduce worker exposure to that allergen by occupational hygiene measures. In Ontario, where isocyanates are a common cause of OA, the *Regulation Respecting Isocyanates* made under the *Occupational Health and Safety Act* requires that workers exposed to this be regularly screened with a respiratory questionnaire and spirometry (53). This screening may be performed by a company physician or by the worker's personal physician. In addition, there are legislated limits for isocyanate levels in the workplace and requirements for monitoring of such levels and employee education regarding health risks of isocyanates. The value of worker surveillance programs is unproven. Although there is some information to suggest that such programs are associated with an earlier diagnosis of OA (54), their value has not been objectively assessed in a prospective manner. Also, even control of a sensitizer to levels that are considered to be generally safe and within legislated allowable limits may not entirely prevent sensitization.

Airway disease from cotton dust and grain dust exhibits different features from OA. Other occupational lung diseases should also be distinguished from OA.

Other occupational lung diseases should be considered in the differential diagnosis, such as byssinosis and grain dust-related airway disease. These lung diseases are generally regarded as separate entities from OA, and are probably associated with endotoxin inhalation. They are often associated with an irreversible obstructive component (55,56). Exposure history is essential to these diagnoses. Similarly, pot-room asthma related to work with exposure to aluminum fluorides is usually considered to be a separate condition from OA, and has very seldom been reported in Canada. Most reports have been from Scandinavia, and the causative agent is unknown (57,58). Hypersensitivity pneumonitis can occur with or without a component of airway hyper-responsiveness to the relevant antigen and should be considered in patients with interstitial lung disease.

RECOMMENDATIONS AND LEVELS OF EVIDENCE

4. A high level accidental exposure coinciding with the onset of asthma should lead to assessment for RADS or irritant-induced asthma. Level 2A (14-18)
5. A definite, objective diagnosis of the work relationship should be made before advising the patient to leave his or her job, and the patient should be referred to a specialized centre. Level 3A (1,20,48,49, and committee consensus)
6. Asthma, ie, variable airflow obstruction or airway hyper-responsiveness, must be objectively assessed with pulmonary function tests (spirometry pre- and postbronchodilator and, if normal, a histamine or methacholine challenge). These tests are most effective in diagnosing or excluding asthma if performed when the patient has symptoms (for spirometry) or within 24 h after the patient is symptomatic (histamine or methacholine challenges). If performed at a time when the patient has been off work and the tests are normal, they should be repeated when the patient is back at work. Level 2A (1,20,21,28,29 and committee consensus)
7. Although patient monitoring of serial peak expiratory flow readings is effort-dependent and compliance may be poor, recordings four times a day for several weeks at work and away from work can be useful to support or rule out OA caused by a sensitizer or aggravation of asthma when used in conjunction with other investigations. This testing can be initiated by the primary care physician or occupational physician, while arrangements are being made for specialist assessment. Level 2B (26-35)
8. Early referral to a specialist in occupational lung disease is needed for most patients with suspected OA because diagnosis is often complex. Rapid access to such specialists is needed, if possible while the patient is still at work. Level 3A (26-39 and committee consensus)
9. Skin testing or other immunological tests with most workplace allergens are not generally available or well standardized, and can be difficult to interpret. Repeat assessments of methacholine or histamine responsiveness while working and away from work have relatively low sensitivity for OA. Assessment of methacholine or histamine responsiveness can be affected by confounding factors. Specific chamber challenges with workplace agents are likely to provide a definitive diagnosis but need specialized facilities that are only available in a few Canadian centres. Level 3A (20-39)
10. General management of the patient's asthma should conform with the recent Canadian guidelines in relation to general and specific environmental control measures and the use of appropriate medications and patient education. Level 3A (3)

1. Suspect OA in all adult-onset asthmatics whose asthma began while working. Level 2A (8-12)
2. Consider an occupational role (cause or aggravation) in all working asthmatics. Level 2A (8-12)
3. The history of asthma worsening at work or following work shifts, or improvement during weekends or holidays off work, while not specific, is a sensitive indicator for OA from a sensitizer and occupational aggravation of asthma. Level 2A (13,19)

11. Where there is reasonable support for a diagnosis of OA and the patient is eligible to apply for workers' compensation, the physician has a responsibility to initiate such a claim with the agreement of the patient. If the patient's asthma can be adequately controlled, the patient should be advised not to give up his or her job until a claim decision is reached. If asthma control cannot be achieved, the patient should be off work on sickness benefits pending a workers' compensation board decision. Level 3A (committee consensus)
12. Patients with confirmed OA due to a sensitizer should have no further respiratory exposure to that agent. The best medical prognosis is achieved with early and complete removal from exposure after a definitive diagnosis is reached. Level 2A (13,49,50)
13. Patients with asthma caused by a high level respiratory irritant exposure (RADS or irritant-induced asthma) can continue to work with precautions to avoid similar accidental exposures. Level 3A (committee consensus)
14. Diagnosis of OA due to a sensitizer should be considered as a 'sentinal event'. Collaborative efforts should be made with occupational physicians and company management to identify other cases of OA in those exposed to the sensitizer, and occupational hygiene measures should be taken to avoid or limit worker exposure. Level 3A (1,20,52).
15. For some workplace sensitizers, routine worker surveillance has been recommended, eg, di-isocyanate exposure in Ontario. The value of this is unproven, although OA in Ontario has been diagnosed earlier in companies with surveillance programs in place. Level 2B (53,54).

CONCLUSIONS

OA should be suspected in all adult onset asthmatics whose asthma begins or worsens while they are working. Early, accurate diagnosis and changes in workplace exposure often lead to clearing of asthma. The diagnosis of OA in co-workers and prevention of OA in other workers are further benefits of appropriate investigation and management.

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