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## REVIEW

# Management and prevention of occupational asthma

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### ABSTRACT

Occupational asthma is a potential preventable form of asthma. This review of diagnosis, management and prevention focuses mainly on publications from the past three years. Early suspicion of the diagnosis is essential for a timely diagnosis and management and the possibility may first be raised by the patient or may need to be elicited by careful history by the health care provider. Objective diagnostic steps are needed, as have been detailed in consensus statements and guidelines. A combination of tests is often needed for diagnosis and these are most easily obtained while the patient is still employed. Management includes consideration of safe future workplace accommodation and of preventive measures for the patient and for other workers.

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**Key words:** Occupational asthma - Diagnosis - Disease management - Prevention and control.

Occupational asthma (OA) is defined as asthma that is caused by work exposures (in contrast to work-exacerbated asthma which is worsened but not caused by work).<sup>1</sup> OA is most often caused by sensitization to a specific workplace agent that may be a high-molecular weight allergen via an IgE-mediated response, or a low-molecular weight chemical sensitizer via an IgE-mediated or other presumed Th2 immunologic response. Less commonly OA can be caused by irritant exposures: irritant-induced occupational asthma, most clearly when criteria for reactive airways dysfunction syndrome (RADS) are met,<sup>2</sup> but also potentially from lower or recurrent irritant exposures.<sup>3</sup>

Management of OA includes diagnosis and treatment for an individual patient and prevention for the wider working population. The diagnosis of OA should be regarded as a sentinel event and should lead to consideration of other workers in the same environment who may

also be affected or at risk of developing OA, and also workers in other environments with the same exposure. Therefore, it is a diagnosis with public health implications. It also is a diagnosis with potential compensation implications and can lead to potential adversarial issues between the worker, employer, and workers compensation systems. Thus, the diagnosis should be made as objectively as possible, and preventive measures can result in widespread benefits.

This review focuses on published articles from 2014 to 2016 as identified from a PubMed search using the search term “occupational asthma”.

### Diagnosis of sensitizer-induced OA

The overall approach to diagnosis has been detailed in Consensus Statements, and guidelines such as those from the American College

of Chest Physicians in 2008<sup>4</sup> and European guidelines in 2012<sup>5</sup>, with similar suggestions for diagnostic steps. Recent reviews have also been consistent with the approach recommended from these Consensus Statements or Guidelines.<sup>1, 6-11</sup> The diagnosis will not be suspected in a patient with asthma unless an occupational history is taken and information obtained that suggests a work association to symptoms. Although this should be simple, there are often significant delays in the primary care provider suspicion of a work association, often several years after the onset of work-related asthma.<sup>12</sup> This may be due to a lack of enquiry by the primary care provider as to asthma symptoms starting or worsening with work and/or improving when away from work or on holiday. Several studies have demonstrated a common lack by primary care providers to ask patients about their work and work associations.<sup>13, 14</sup> Other factors associated with delay include fear by the patient to admit a work relationship, due to concern as to possible job loss or income loss and lack of awareness by the patient that their work could cause or affect asthma.<sup>14, 15</sup> In an attempt to improve the time to diagnosis in the primary care setting, potentially questions for patients with asthma could be incorporated into electronic medical records, and initial studies suggest feasibility of this approach.<sup>16, 17</sup> Questions that have shown greatest sensitivity for sensitizer-induced OA from high-molecular weight sensitizers are symptoms of wheezing worse at work and better off work, absence of accompanying dysphonia, and the presence of associated symptoms of allergic rhinitis or conjunctivitis, but these questions were not predictive for OA from low-molecular weight agents.<sup>18</sup> In some patients work-related asthma or eosinophilic bronchitis may present as a chronic dry cough.<sup>19</sup> An older study showed that reported improvement in asthma symptoms away from work and worsening when back at work was sensitive (88%) but had poor specificity for OA.<sup>20</sup> However, inclusion of these questions would not prevent denial of symptoms due to concerns regarding socio-economic factors such as job loss and income loss: concerns that

may not be adequately assuaged by workers' compensation awards. Information of the job performed and the exposures at work may be helpful in suspecting OA, but since there are over 300 reported causes of sensitizer-induced OA,<sup>21</sup> the absence of a recognized sensitizer at work does not exclude the diagnosis. Exposures that may induce irritant-induced OA are accidental exposures to agents that are expected to be irritant, such as acidic or alkaline dusts or fumes, smoke or irritant gases.

After suspicion of OA from the history, an objective diagnosis of asthma is needed by demonstrating a significant bronchodilator response or airway hyperresponsiveness since there can be other causes of similar symptoms such as laryngeal syndromes, gastroesophageal reflux, and rhinitis. Eosinophilic bronchitis should also be considered in patients with asthma-like symptoms without pulmonary function changes, and can also have an occupational cause. It should be investigated with induced sputum cytology.<sup>22</sup> Tests for asthma can be falsely negative if performed after a period away from work or away from the causative exposure, so these tests are preferably performed within 24 hours of typical work exposure. A normal methacholine test in a patient still exposed to the implicated work agent was shown to have a negative predictive value of 98%, although, as expected the sensitivity for the diagnosis of OA was low, 39%.<sup>23</sup>

Functional changes in asthma at work *versus* off work can be assessed with recording of serial peak expiratory flow readings, symptoms and bronchodilator use during periods at work and off work. Assessment of changes in methacholine PC20 after a period off work compared with results after typical days at work, and when feasible induced sputum eosinophil counts during a period of work *versus* off work can be helpful and concordant changes in these may be sufficient to support or exclude a diagnosis of sensitizer-induced OA.

When available, immunologic tests are also useful to indicate the presence or absence of sensitization to a high-molecular weight work allergen.<sup>4</sup> Specific IgE antibodies to a relevant occupational allergen can indicate sensitiza-

tion but alone are not sufficient to confirm OA since a proportion of exposed but asymptomatic workers can be sensitized. Although skin prick tests are simple and quick to perform, there are limited commercial skin test extracts for occupational allergens and among those available, most are not standardized. Similarly, there are limited available reliable tests for *in vitro* assessment of specific IgE antibodies to occupational allergens. A few centers have reliable assays for specific IgE for low-molecular weight antigens such as diisocyanates<sup>24</sup> and acid anhydrides.<sup>25</sup> If positive these increase the probability of OA. *In vitro* assessment of IgE antibodies to specific protein components within an allergen extract can potentially distinguish occupational allergic responses to natural rubber latex from cross reacting responses from fruit allergy,<sup>26</sup> but at present these are not readily available for clinical use. Other *in-vitro* tests that have been used to assess specific sensitization include the basophil activation test,<sup>27, 28</sup> but this requires a fresh blood sample and is also not widely available.

Once suspected from the history, the diagnosis of sensitizer-induced OA can often be made with a combination of the above investigations. Details of the work exposure may not be known by the patient, but patients are entitled to copies of material safety data sheets from the workplace that can be helpful although they do not always provide complete information. Additional helpful information on likely exposures may be provided by an occupational hygienist if available,<sup>29</sup> or by reports from workplace surveys. This is especially important if specific challenge tests are needed for confirmation of the diagnosis, if the diagnosis has not been confirmed by other investigations.<sup>29</sup> Specific challenges require specialized facilities and if performed, should meet current recommendations.<sup>30</sup>

### Diagnosis of irritant-induced OA

The diagnosis of irritant-induced OA is largely circumstantial. It is most probable when the new-onset of asthma coincides with an exposure at work that was likely high-level

and an expected respiratory irritant, in a patient with no previous lung disease. When the criteria for RADS<sup>2</sup> are met, the diagnosis is very probable. Asthma may be objectively assessed by bronchodilator responsiveness and/or methacholine challenge, absence of previous lung disease documented by chart review, and there may be objective confirmation of the exposure, but there are no additional tests to confirm the diagnosis. When RADS criteria are not fully met (*e.g.*, onset of asthma symptoms more than 24 hours after the exposure, more than one non-massive exposure, or duration of symptoms less than 3 months), then the probability of irritant-induced asthma is less certain.<sup>3</sup> Even lower clinical certainty exists for the diagnosis of "low-level irritant-induced asthma" which is mainly based on probabilities of asthma determined in epidemiologic studies (*e.g.* with exposure to cleaning products such as bleach),<sup>31-33</sup> and there are no objective tests to distinguish this from the coincidental onset of asthma for an individual patient.<sup>3</sup>

### Management of OA after diagnosis

#### *General asthma management*

For patients with OA, general management of asthma comprises control of exposure to relevant environmental triggers (in addition to the workplace triggers), and appropriate pharmacologic medications as for patients with asthma that is not work-related.<sup>4, 34</sup>

#### *Work-related management*

Patients with confirmed sensitizer-induced OA should be completely removed from further exposure to the causative work sensitizer for the best outcome of their asthma.<sup>34, 35</sup> This may sometimes be achieved by a change in job within the same workplace, but often requires a change in employer. Reduction of exposure but not complete avoidance of exposure has not been shown to be as effective for asthma prognosis.<sup>34, 35</sup>

Even with complete removal from exposure to the causative agent, although most patients

have an improvement in asthma severity (with improvement occurring up to several years after removal),<sup>36</sup> a systematic review found only a minority have complete symptomatic clearing of asthma, 32% at 31 months, using a pooled estimate<sup>36</sup> and 73% had persisting airway hyperresponsiveness. Within study comparisons from that systematic review suggested that a shorter duration of symptoms at work was associated with better outcomes<sup>36</sup> and a later literature review<sup>37</sup> indicated that an early diagnosis and early intervention<sup>38</sup> as well as milder asthma at the time of diagnosis<sup>39</sup> provides best outcomes for asthma and has been advocated. Older age and high molecular weight sensitizers have been associated with worse prognosis.<sup>37</sup> Following diagnosis of sensitizer-induced OA and management including removal from further exposure, a significant reduction has also been shown in asthma exacerbations and the need for health-care utilization in Ontario and Quebec.<sup>12</sup>

#### *Socioeconomic outcomes*

Although asthma improves in patients with sensitizer-induced OA who are removed from further exposure to the relevant sensitizer, there can be a significant negative psycho-socioeconomic impact. To some extent this may be mitigated by support from workers' compensation systems but studies from several countries have shown that even with workers' compensation support there can be significant economic loss, in up to 62% of those with OA,<sup>40, 41</sup> and increases in anxiety and depression<sup>42, 43</sup> that are associated with the diagnosis, and even with the suspected diagnosis. These factors also need to be considered in management of these patients.<sup>44</sup>

#### *Management of irritant-induced OA*

Workplace management differs for patients with irritant-induced OA, since they may be able to return to the same workplace area if they will not be exposed again to the same exposure conditions that caused their asthma. However, if the patient has persisting asthma,

then potentially exposures at work could exacerbate asthma (work-exacerbated asthma) as for patients who have asthma for any other reason.<sup>4</sup>

### **OA prevention**

Preventive measures are part of the general management of OA, to reduce the public health impact of OA by reducing incidence (by primary preventive measures), to protect other workers who have not developed OA (primary prevention) and to detect it early and intervene, preferably before there is significant disease (secondary prevention). Finally, tertiary preventive measures reduce the impact of OA for the individual worker by appropriate treatment (tertiary prevention).

OA should be considered as a sentinel diagnosis, providing an opportunity to identify other affected workers and to introduce preventive measures. This might be achieved by notification of the company's occupational physician with the approval of the patient, or by notification of an organization such as a provincial Ministry of Labor (in Canada) or Occupational Safety and Health Association (OSHA) in the USA. Voluntary physician reporting from surveillance systems such as SWORD<sup>45</sup> or SHIELD<sup>46</sup> in the UK or from the SENSOR surveillance system<sup>47</sup> that is active in some US states and European surveillance reviews<sup>48</sup> can also indicate relative changes in rates of OA and/or which jobs and exposures are associated with increasing rates of OA in the reporting area, that may lead to preventive interventions. Similarly, telephone surveys such as performed by the Center for Disease Control<sup>49</sup> or published reviews of workers' compensation claim data<sup>50</sup> or occupational asthma clinic reviews<sup>51</sup> can serve to indicate likely prevalence or incidence rates or relative rates of specific causes. As an example, diisocyanates have been the most common single group of sensitizers causing OA in many industrialized areas for several years, but surveys have shown that preventive measures have been associated with marked reductions in new cases in several countries.<sup>50, 52</sup>

Preventive measures differ somewhat for sensitizer-induced and irritant-induced OA and will be divided into primary, secondary and tertiary measures.

### OA from a sensitizer

#### *Primary preventive measures*

Although individual risk factors have been identified, such as atopy as a risk factor for sensitization to wheat allergens and natural rubber latex,<sup>53-55</sup> and some genetic associations have been described for diisocyanates,<sup>56-60</sup> nevertheless at present host factors are not sufficiently sensitive or specific to predict which workers have a high risk of sensitization.

An ideal (but usually not practical) preventive measure would be the complete avoidance of inhalation of respiratory sensitizing agents in the workplace. There are many high-molecular weight sensitizers (proteins) for which elimination would not be desired or practical (such as most animal and plant allergens). Similarly, many low-molecular weight sensitizing agents cannot readily be removed from use and replaced with safer agents or safer processes. One example of a process change that has eliminated a source of respiratory sensitization is the switch to digital imaging instead of the processing and developing of films, both in the commercial setting (films from cameras) and in health care (radiographic imaging).

An example of substitution of a chemical has been the replacement of glutaraldehyde with orthophthalaldehyde, *e.g.* for sterilization of endoscopes. Although risks appear to be less with orthophthalaldehyde, there subsequently have been a few cases of sensitization leading to OA from this.<sup>61</sup>

An excellent example of the value of primary prevention is found with OA from natural rubber latex (NRL). This was relatively common in the early 1990s when NRL gloves were widely used, especially in health care facilities for reduction of transmissible infections,<sup>54, 62, 63</sup> but also were widely used in by food handlers and cleaning staff. Elimination of NRL gloves and substitution with non-latex gloves was feasible

in some setting where NRL gloves were previously used, such as for hospital housekeeping staff and food handlers. In addition, a combination of interventions has led to marked reduction or elimination of exposure to airborne NRL allergens from powdered latex gloves. Measures have ranged from improvements in manufacturing to leach out the NRL proteins from the gloves to produce low-protein gloves, and to reduce the glove powder that transmitted NRL proteins into the air during donning and removal of gloves.<sup>64, 65</sup> The resulting low-protein, low-powder NRL gloves carry much less risk of sensitization to NRL proteins.<sup>65</sup> In addition, there have been workplace changes to reduce the unnecessary use of NRL gloves and then replacing them with non-latex gloves has also reduced co-worker-exposure to NRL proteins.<sup>66</sup> Education measures for workplaces and workers concerning their risks of allergy and asthma from NRL gloves, and means to reduce risks have also been introduced in many countries.<sup>67, 68</sup> This combination of interventions to reduce exposure has been associated with substantial reduction in incidence of NRL allergy and OA.<sup>69-71</sup>

Another example of interventions to reduce exposure to airborne high-molecular weight occupational allergens is the introduction of improved laboratory animal cage ventilation in laboratory animal care facilities to reduce exposures to small mammal airborne proteins, such as by automatic cage cleaning, housing animal in cabinets with exhaust ventilation and handling of animals on ventilated benches and use of central vacuum cleaners as well as by use of respiratory protective devices.<sup>72</sup> Among laboratory workers exposed to rats, increasing level of exposure to rat urinary allergen was associated with the risk of allergic symptoms,<sup>73</sup> although highest exposures have been associated with lower risk, perhaps from a healthy worker effect.<sup>74</sup>

Similarly, process changes can reduce exposure to flour in bakeries, such as lids for mixing containers, using a divider oil, and avoiding dry sweeping of flour.<sup>75</sup> This South African research group also showed a bell-shaped pattern of exposure-response with lower risk at

highest exposure levels that was attributed to a healthy worker effect.<sup>76</sup>

Legislated limits to allowable airborne concentrations of specific chemicals, if enforced, can also control workplace exposures, such as the limits set in Ontario for diisocyanates by the Ontario Ministry of Labor with associated requirements for monitoring of exposure levels.<sup>77</sup> Other occupational hygiene measures that have been used in workplaces to reduce exposures include confinement of processes that generate potential high concentrations of sensitizers such as diisocyanates, adequate ventilation, use of robots rather than workers, and finally use of appropriate well-fitting respiratory protective devices (recognizing that it is generally not appropriate to expect workers to use these throughout a work shift).

Although risks of developing OA generally increase with greater exposure to the respiratory sensitizer, there is no clear lower cut-off level of exposure (other than no exposure) that will prevent OA in all workers.

Skin exposure to sensitizing chemicals has also been implicated in the development of sensitization and subsequent OA, based on animal studies and a few studies of OA from diisocyanates.<sup>78</sup> Therefore, skin protection has also been recommended to reduce risks.

Education of workers is also a component of primary prevention for OA. Adherence to the preventive measures to reduce exposure as illustrated above is likely to improve with understanding of the risks of exposure and the rationale for the preventive measures. This may be performed by the health and safety personnel of a company or by an external agency, and may be supplemented from public education through unions, health and safety organizations and lung associations. Potentially web-based educational tools may be helpful.<sup>79, 80</sup> In addition, health care providers could also increase awareness of risks by obtaining an occupational history and providing advice to their patients.<sup>14, 81</sup>

### *Secondary preventive measures*

Secondary prevention comprises the early detection of sensitization and/or OA since

early detection and intervention to prevent further exposure offers the best medical prognosis. Medical surveillance programs arranged through the employer may include pre-placement and periodic questionnaires to identify upper and lower respiratory symptoms, spirometry and immunologic tests (skin prick tests or serologic tests of specific IgE antibodies) as feasible.<sup>81</sup> For example, skin tests or specific IgE may be assessed for laboratory animal workers, detergent workers (or others with exposure to enzymes at work), bakers, and others working with high molecular weight sensitizers. In addition specific IgE can be assessed for a few low-molecular weight sensitizers such as complex platinum salts and acid anhydrides. For these workers, the identification of specific IgE antibodies does not by itself indicate a diagnosis of OA but should lead to further medical assessment. In the example of complex platinum salts, a positive skin test appears to indicate a high risk of developing OA<sup>82</sup> and the recommendation has been made to remove workers with a positive skin test from further exposure to platinum salts even in the absence of symptoms<sup>83</sup> since those who develop asthma usually do not have clearing of their asthma after removal from exposure. Development of new respiratory symptoms or changes on spirometry in a surveillance program should also prompt further medical evaluation.

Within medical surveillance programs, the value of spirometry appears to be less than the value of the symptom questionnaire,<sup>84, 85</sup> though the performance of spirometry may provide an additional opportunity to reinforce knowledge regarding protective measures, sensitization and OA.

The value of medical surveillance programs for OA including skin testing has been demonstrated in platinum workers,<sup>82</sup> and for workers exposed to enzymes such as in the detergent industry.<sup>86</sup> Skin tests or serum specific IgE can also be included with questionnaires in surveillance programs for high-molecular weight sensitizers such as bakery workers<sup>87</sup> although routine surveillance has been suggested to underestimate the incidence of sensitization as compared with research surveys,<sup>87</sup> perhaps

from lack of disclosure of symptoms due to fear of job loss.<sup>88</sup> Other exposures for which immunologic tests can be included in surveillance programs include laboratory animal workers, and a few chemical sensitizers such as acid anhydrides.<sup>89</sup>

Medical surveillance programs for diisocyanates (pre-placement and periodic questionnaires and spirometry) in Ontario and Quebec have been associated with an earlier diagnosis of OA.<sup>50, 90</sup> However, as with many occupational studies, in the example of diisocyanates there have been several overlapping changes in workplaces that may have contributed to the observed reductions in reported incidence of OA. These include: changes from predominant use of volatile toluene diisocyanates to less volatile forms such as methylene diphenyl diisocyanate; increased use of robotics; mandated air exposure limits; spray booths and air-supply respirators for spray-painters; in addition to the medical surveillance program.

Medical surveillance could also include early suspicion of OA by health care providers. OA from high molecular weight sensitizers is often preceded by occupational allergic rhinitis and/or conjunctivitis.<sup>55</sup> Enquiry by the health care provider as to the association between the workplace and upper or lower respiratory symptoms may lead to an earlier diagnosis. Patients with OA have reported that factors delaying their diagnosis have included failure of their physician to ask about a work-relationship, and lack of awareness that their work could cause asthma.<sup>14, 15</sup> Similarly, it may be expected that worker-education may lead to an earlier diagnosis.

#### *Primary and secondary prevention of irritant-induced OA*

Primary prevention of irritant-induced OA relies on good occupational hygiene measures in the workplace and education of workers in the safe management of any accidents that can lead to irritant exposures. Appropriate early medical care should be provided to workers who have had exposure to respiratory irritants

in order to document any respiratory effects and provide treatment.<sup>4</sup>

#### *Tertiary prevention of sensitizer-induced and irritant-induced OA*

Tertiary prevention consists of the prevention of morbidity by appropriate management of OA as detailed above.

### Conclusions

The diagnostic approach continues to rely heavily on the medical history for early suspicion of OA, but objective tests are needed for the diagnosis and should be performed early, preferably while the patient is still employed and can be assessed at-work and off-work if sensitizer-induced OA is suspected. Irritant-induced OA is a diagnosis of probability based on the exposure history and the objective evidence of asthma in the absence of preceding lung disease. Management includes that of the individual patient but also consideration of preventive measures for other workers at risk for OA.

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