Work-Related Asthma

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Objective: Summarize developed evidence-based diagnostic and treatment guidelines for work-related asthma (WRA). **Methods:** Comprehensive literature reviews conducted with article critiquing and grading. Guidelines developed by a multidisciplinary expert panel and peer-reviewed. **Results:** Evidence supports spirometric testing as an essential early test. Serial peak expiratory flow rates measurement is moderately recommended for employees diagnosed with asthma to establish work-relatedness. Bronchial provocation testing is moderately recommended. IgE and skin prick testing for specific high-molecular weight (HMW) antigens are highly recommended. IgG testing for HMW antigens, IgE testing for low-molecular weight antigens, and nitric oxide testing for diagnosis are not recommended. Removal from exposure is associated with the highest probability of improvement, but may not lead to complete recovery. **Conclusion:** Quality evidence supports these clinical practice recommendations. The guidelines may be useful to providers who diagnose and/or treat WRA.

INTRODUCTION

Asthma is a common, chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation with increased airway responsiveness to a variety of stimuli being typical.[1–5] Work-related asthma (WRA) includes both asthma of an occupational origin (occupational asthma [OA]) and work-exacerbated asthma (WEA). OA includes sensitizer-induced asthma, resulting from sensitization to an antigen in the workplace, and irritant-induced asthma, induced by workplace exposures to irritants (Table 1). Each condition has the potential for considerable acute morbidity, long-term disability, and adverse impact on income and quality of life.[6–12]

The most common form of occupational lung disease in many industrialized countries, with approximately 10% to 15% of all prevalent adult cases attributed to occupational factors,[6–8,10,12–14] OA is further classified into OA with latency or OA without latency. OA without latency is less common, and is believed to represent 5% to 15% of all OA cases.[1,15] The percentage of new-onset adult asthma attributable to occupational causes is considered to be much higher, up to a third of all cases.[16,17] The frequency of WEA, defined as preexisting reactive airways disease that is made temporarily or permanently worse due to occupational exposures, is substantially more common than OA.[18]

The predisposing factors for developing OA with latency are not well known. Atopy is the primary established risk factor, operating largely with respect to high molecular weight (HMW) antigens such as animal proteins. It has been proposed that human leukocyte antigen class-2 alleles may be a risk factor for the development of OA resulting from low molecular weight agents.[11,19,20] Medical management and compensation decisions require a thorough assessment of suspected OA, which may be mistaken for non-OA unless a detailed history, including occupational history, and appropriate medical tests are performed to support an association with work.[21]

GUIDELINE FOCUS/TARGET POPULATION

The American College of Occupational and Environmental Medicine (ACOEM) created its evidence-based Work-related Asthma Guideline to primarily address diagnostic options to help determine whether an employee has asthma, and whether the asthma is related to workplace exposures (Fig. 1). It was designed to present health care providers—who are the primary target users—with evidence-based guidance on the evaluation and treatment of WRA. This report summarizes findings from that Guideline (138 pages, 497 references) and addresses the following questions developed by the Evidence-based Work-related Asthma Panel:

1. Is there evidence on how to identify workers who are at higher risk of developing occupational asthma?
2. What evidence is there for the diagnosis of occupational asthma?
3. Is there evidence that different diagnostic modalities are needed for workers with new onset of symptoms or worsening of previous asthma symptoms?
4. Are there diagnostic tests that can assist in differentiating occupationally related asthma from nonoccupational asthma?
5. Is there evidence on treatment options that differ for occupationally related asthma from nonoccupational asthma?
6. What management options are available for occupational asthma?
7. Is removal from work necessary in all cases of occupationally related asthma?

The primary target population is working-age adults, although the literature searches included articles addressing all adults. Thus, it is recognized that the principles may apply more broadly.

GUIDELINE DEVELOPMENT PROCESS

A detailed methodology document specified evidence selection, scoring, incorporation of cost considerations, and formulation of recommendations.[22,23] The aim was to identify the highest quality evidence on any given topic. Guidance was drafted using tables that abstracted the evidence and which were forwarded to the multidisciplinary Panel that reviewed the evidence and finalized the text and recommendations.

EVIDENCE REVIEW AND GRADING

All evidence related to WRA in searching four databases (*PubMed*, *EBSCO*, *Cochrane Library*, and *Scopus*) was included in this guideline. The comprehensive searches for evidence were performed through September 2012 for diagnostic studies and February 2014 for management studies to help ensure complete study capture. The search strategies retrieved a total of 10,598 articles that were screened, with all potentially appropriate study abstracts reviewed and evaluated against specified inclusion and

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The authors declare no conflicts of interest.

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TABLE 1. Types of Work-Related Asthma

Nomenclature	Term	Defining Features
Sensitizer-induced OA	OA with latency of allergic or presumed immunological mechanism: not necessarily IgE	Immunological/hypersensitivity component and diagnostic tests include measures of specific sensitization (eg, skin-prick test, serum specific IgE, circulating IgC against the antigen or skin sensitization)
Irritant-induced OA	OA without latency	No allergic component and worker is not sensitized to an agent; rather, the agent causes inflammatory responses through irritant mechanisms
WEA or aggravated asthma	WEA or aggravated asthma (no latency period)	Worker has prior or concurrent history of asthma not induced by that workplace. The worker is not sensitized to an agent at work, but is irritated by a ''non-massive'' exposure (eg, cold, exercise, non-sensitizing dust, fumes, or sprays) that provokes an asthmatic reaction

IgE, immunoglobulin E; OA, occupational asthma; WEA, work-exacerbated asthma. Adapted from the American College of Chest Physicians.

exclusion criteria. Searches were supplemented with articles from personal files and reference reviews. A total of 497 articles were retrieved of which 157 met the inclusion criteria. Of those, 114 were included as high- or moderate-quality studies in evidence-based guideline development. The remaining 43 studies were deemed low-quality and excluded.

All included studies were scored for quality. Recommendations were graded from (A) to (C) in favor and against the specific diagnostic test or treatment, with (A) level recommendations having the highest quality body of literature. Quality evidence was developed into evidence-based recommendations. Expert consensus was employed for insufficient evidence (I) to develop consensus guidance. Recommendations and evidence tables were reviewed and amended by the multidisciplinary Panel. This guideline achieved 100% Panel agreement for all developed guidance.

COMMENTS AND MODIFICATION

Guidance was developed with sufficient detail to facilitate assessment of compliance (Institute of Medicine [IOM]) and auditing/monitoring (Appraisal of Guidelines for Research and Evaluation).[24,25] Alternative options to manage conditions are provided in other ACOEM guidelines when comparative trials are available. The only Appraisal of Guidelines for Research and Evaluation[25] and IOM criterion[24] not followed was incorporation of the views of the target population. In accordance with the IOM's *Trustworthy Guidelines*, this guideline underwent external peer review by four external reviewers, and subsequent revisions to the guidance, and detailed records of the peer-review processes have been kept, including responses to external peer reviewers.[24]

This guideline is updated at least every 3 years or more frequently should evidence require it. All treatment recommendations are guidance based on synthesis of the evidence plus expert consensus. These recommendations are for practitioners, and decisions to adopt a particular course of action must be made by trained practitioners on the basis of available resources and the particular circumstances presented by the individual patient.

CLINICAL RECOMMENDATIONS

Sixteen diagnostic recommendations were formulated for diagnostic testing, of which 11 were ultimately recommended and five were not recommended (Table 2). There were nine recommendations formulated for the management of WRA, of which five were recommended and four were not (Table 3).

SPIROMETRY TESTING

Spirometry, performed alone or in conjunction with pre- and postbronchodilator testing, is an important component of the evaluation and management of persons with possible WRA.[26–32] Spirometry with bronchodilator administration has three distinct potential roles when WRA is a concern:

1. Determining whether asthma is present;
2. If asthma is present, helping inform the conclusion about whether the asthma is work related; and
3. Monitoring response to therapy and possible return to work.

Spirometry with bronchodilator is not invasive, has few adverse effects, and is low-to-moderate cost and high in yield for complications and other respiratory problems. As its value lies in correlation with clinical information and observation, spirometry with bronchodilator is a recommended integral part of the evaluation of WRA.

PEAK EXPIRATORY FLOW RATES

Serial peak expiratory flow rate monitoring is moderately recommended (evidence level B) to diagnose WRA in patients already diagnosed with asthma by other methods. Six moderate-quality studies support the use of peak expiratory flow rate for the diagnosis of OA and WRA; however, peak expiratory flow rate is heavily dependent upon the worker's efforts and assumes worker honesty in performing and recording the test results.[33–40]

NONSPECIFIC BRONCHIAL PROVOCATION TESTING

Nonspecific bronchial provocation testing has been evaluated in quality studies that utilized methacholine, histamine, and mannitol as provocative testing agents. Four high-quality and 12 moderate-quality studies were used in formulating recommendations of nonspecific bronchial provocation testing as an investigational tool for the diagnoses of OA and WRA.[41–57] Nonspecific bronchial provocation testing is strongly recommended (evidence level A) to diagnose general asthma, and moderately recommended (evidence level B) to diagnose WRA. The Panel supports the American Thoracic Society's guideline for interpreting the methacholine dose that would result in a positive test.[58]

SPECIFIC IMMUNOLOGICAL TESTING

Specific immunological testing was evaluated separately for HMW and low molecular weight antigens. There were six high- and 12 moderate-quality studies used in the formulation of recommendations for specific immunological testing.[50,51,57,59–73] The Panel evaluated the difference between immunoglobulin E (IgE) and IgG tests. IgE testing for HMW antigens is strongly recommended (evidence level A) when specific testing reagents have been validated and are commercially available. Testing of IgG for HMW antigens is not recommended (evidence level C) for use as a diagnostic tool; however, this test may be efficacious as a marker for exposure to the antigen. IgE testing to low molecular weight antigens is not recommended (evidence level I).

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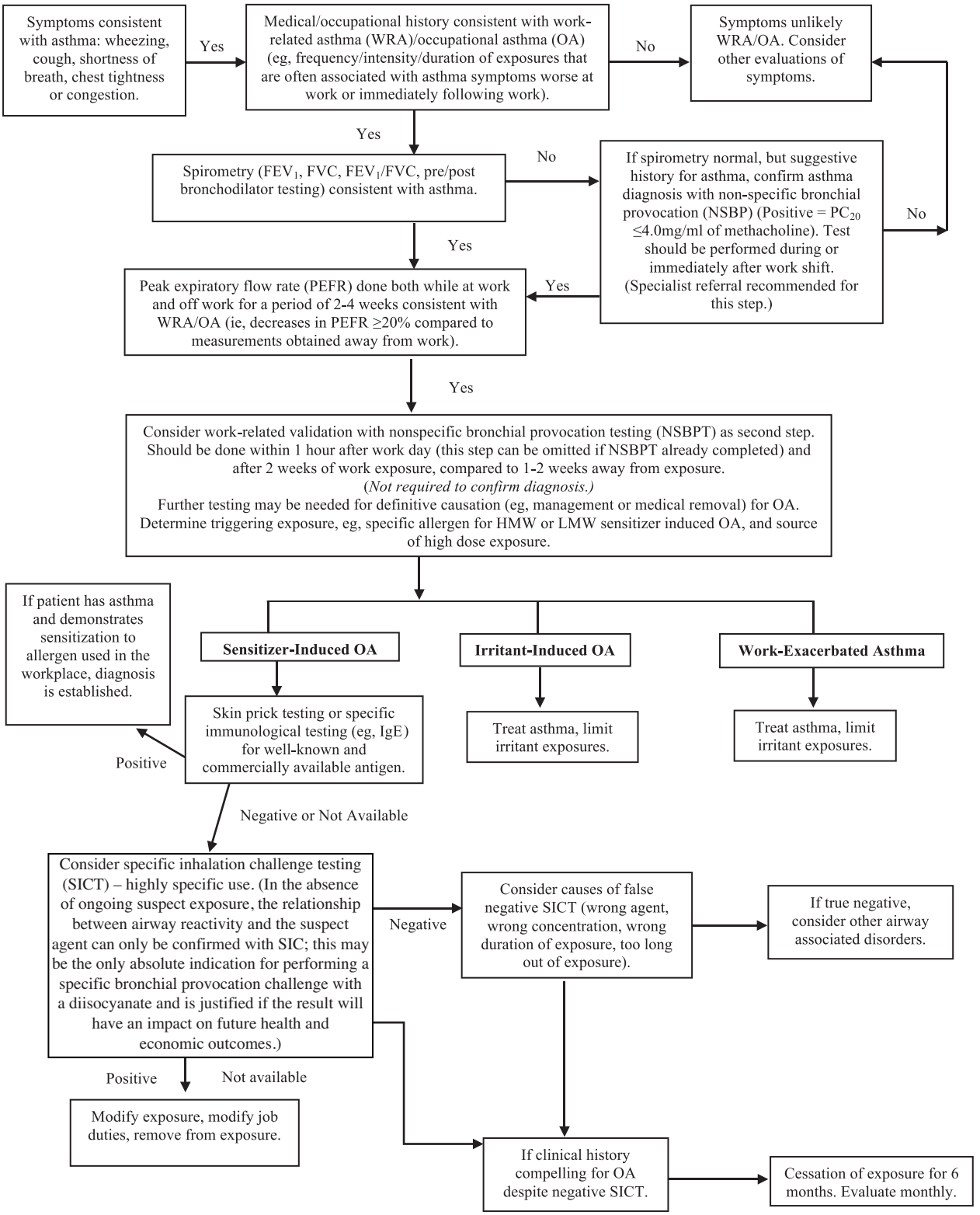

FIGURE 1. Diagnostic evaluation of occupational asthma with continuing exposure.

SKIN-PRICK TESTING

Skin-prick testing (SPT) was evaluated separately for HMW and low molecular weight allergens. There were eight high- and 12 moderate-quality studies used to formulate recommendations for SPT.[50,51,53,62,73–88] SPT for HMW allergens is strongly recommended (evidence level A) for allergens that are commercially available and validated. Current commercially available validated extracts include some for natural rubber latex, wheat flour,

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TABLE 2. Summary of Recommendations for Diagnostic Testing for Asthma

Test	Recommendation(s)
Peak expiratory flow rates	Serial peak expiratory flow measurements as an initial evaluation method for diagnosing work-related asthma, in patients already diagnosed with asthma by other methods—Moderately Recommended, Evidence (B)
Nonspecific bronchial provocation testing	Nonspecific bronchial provocation testing (eg, methacholine) for use in diagnosing asthma, if the clinical history is compelling, and other tests (spirometry and bronchodilator responsiveness) are unhelpful—Strongly Recommended, Evidence (A)
	Nonspecific bronchial provocation testing (eg, methacholine) for use in diagnosing WRA, as other steps are required to establish the work-relatedness of the asthma—Moderately Recommended, Evidence (B)
	Mannitol bronchial provocation testing for use in diagnosing WRA; other steps are required to establish the work-relatedness of the asthma—Recommended, Evidence (C)
Specific immunological testing	Specific immunological testing (IgE) for workers with symptoms consistent with OA to certain HMW specific allergens and when standardized antigens and assay protocols exist—Strongly Recommended, Evidence (A)
	Specific immunological testing (IgG) as a diagnostic tool for select workers with symptoms consistent with OA to HMW specific allergens—Not Recommended, Evidence (C)
	Specific immunological testing (IgE) for workers with symptoms consistent with OA to low molecular weight specific allergens due to low sensitivity and specificity and lack of method validation—Not Recommended, Insufficient Evidence (I)
Skin-prick testing	Skin-prick testing for HMW allergens for select workers with symptoms consistent with OA to specific allergens and where validated, commercial skin testing extracts are available—Strongly Recommended, Evidence (A)
	Skin prick testing for low molecular weight allergens for select workers with symptoms consistent with OA to specific allergens, and where skin testing extracts are available—Moderately Recommended, Evidence (B)
	Skin-prick testing for allergens not covered above—Not Recommended, Insufficient Evidence (I)
Specific inhalation challenge testing	Specific inhalation challenge testing for use in diagnosing WRA with latency for highly select cases, where the diagnosis of OA is highly suspected, but has not been established by less invasive means—Recommended, Evidence (C)
Nitric oxide testing	Nitric oxide testing for the diagnosis of OA, as it cannot differentiate between, eg, OA and other eosinophilic lung inflammatory conditions—Not Recommended, Insufficient Evidence (I)
	Exhaled nitric oxide testing for establishing a diagnosis of asthma when more objective evidence is needed such as in litigated cases—Recommended, Evidence (C)
	Exhaled nitric oxide testing for selective use in monitoring airway inflammation in patients with moderate and severe asthma—Moderately Recommended, Evidence (B)
Nasal lavage testing	Nasal lavage for select workers with symptoms consistent with occupational airways allergy to specific allergens—Recommended, Evidence (C)
	Nasal lavage fluid analysis after challenge with the allergen for the diagnosis of OA—Not Recommended, Insufficient Evidence (I)

IgE, immunoglobulin E; HMW, high molecular weight; OA, occupational asthma; WRA, work-related asthma.

rye flour, grain dust, alpha-amylase, bovine danders, and other animal antigens. SPT to low molecular weight antigens is moderately recommended (evidence level B) for allergens that have a commercially available validated test including some available for reactive dyes, halogenated platinum salts, and trimellitic anhydride. All other SPT for allergens not specifically mentioned are not recommended (evidence level I).

SPECIFIC INHALATIONAL CHALLENGE TESTING

Specific inhalational challenge testing is often considered the gold standard test for diagnosing sensitizer-induced OA and is used when other methods have failed to establish the diagnosis. It is also used as a reference standard, as there is no other definitive diagnostic test. Four high- and 16 moderate-quality studies were used to formulate this recommendation.[11,42,46–50,62,63,89–99] However, specific inhalational challenge testing is highly technical and costly and has potential for severe adverse effects, including fatalities. Facilities must have the technological equipment and ability to control exposures, as well as monitor and resuscitate patients, and few such facilities exist. Thus, specific inhalational challenge testing is recommended only under highly select circumstances at appropriately equipped facilities that include direct medical supervision throughout the testing. The highly limited availability of facilities as well as adverse effects caused the Panel to reduce this recommendation from strongly recommended (evidence level A) to recommended (evidence level C).

NITRIC OXIDE TESTING

Nitric oxide testing—also known as fractional exhaled nitric oxide (FENO)—was evaluated as a diagnostic tool for all asthma including OA, and for selective monitoring of asthma treatment and progression. Two high- and 20 moderate-quality studies were used to formulate recommendations for FENO.[45,100–119] FENO is not recommended to diagnose OA (evidence level I) as it cannot differentiate between asthma and other conditions such as eosinophilic inflammatory conditions. FENO is recommended (evidence level C) for diagnosis when more objective evidence is needed such as in litigated cases. FENO is recommended (evidence level B) in monitoring airway inflammation in patients with moderate and severe asthma as evidence indicates it correlates with the disease activity.[104,107,115] Additional guidance regarding criteria for clinically meaningful change and timing for FENO was abstracted from the evidence.[102,118,120–122] It is recommended that a change of 20% in the value is clinically significant and should be measured every 2 to 4 weeks while the treatment plan is being modified and finalized.[104,122,123]

NASAL LAVAGE TESTING

Eight moderate-quality studies were used in formulating recommendations for nasal lavage.[63,93,124–129] Nasal lavage is recommended (evidence level C) for select workers with symptoms consistent with occupational upper airway allergy to specific allergens. The testing supports a diagnosis of occupational allergy, but

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TABLE 3. Summary of Recommendations for Management of Work-Related Asthma

Recommended	Not Recommended
Patients, physicians, and employers be informed that persistence of exposure to the causal agent is likely to result in deterioration of asthma symptoms and airway obstruction. (I)	Reduction of exposure as a strategy for certain low molecular weight asthmagens (diisocyanates). (I) As an alternative to complete elimination of exposure, continued low-level exposure with use of personal protective equipment has been associated with adverse health outcomes including reports of death.
Patients and their physicians be made aware that complete avoidance of exposure is associated with the highest probability of improvement, but may not lead to a complete recovery from asthma. (I)	Reducing exposure to the causal agent as a strategy in the management of sensitizer-induced asthma, as available evidence indicates that most asthma will worsen in continued exposure. (I) However, it is recognized that some workers will insist on remaining in their jobs for social, economic, and professional reasons, despite counseling on the adverse health consequences. Continued exposure, even at low levels, may result in worsening asthma. If such patients remain in exposure, documentation of the recommendation regarding removal is recommended. (I) Required close and careful medical monitoring of such patients is recommended (I) to ensure early identification of worsening asthma. Reducing exposure to the causal agent in addition to providing immunotherapy and other asthma management, where applicable, may be recommended (I), and will depend on the asthmagen, level of exposure, severity of asthma, and the clinical judgment of the physician.
For irritant-induced asthma, exposure reduction to the lowest levels possible and careful medical monitoring should be performed to ensure early identification of worsening asthma. (I)	Use of respiratory protective devices as a safe approach for managing asthma, especially in the long-term and in patients with severe asthma. (I)
Pharmacological treatment of WRA follows general recommendations for asthma (C). Current ERS/ATS recommendations for treatment of severe asthma should be followed.	Anti-asthma medications as a reasonable alternative to environmental interventions such as exposure reduction or medical removal. (I)
Immunotherapy may be considered in settings where OA due to a specific HMW allergen has been established, when only one or a few allergens have been linked clinically to disease, when there is a standardized commercial allergen extract available for treatment, good control with pharmacotherapy cannot be established and the causative agent cannot be completely avoided for economic, professional, or other reasons. (I)	

HMW, high molecular weight; ERS/ATS, European Respiratory Society/American Thoracic Society; OA, occupational asthma; WRA, work-related asthma.

other tests are required to establish a diagnosis of WRA; however, nasal lavage following nasal provocation testing is not recommended (evidence level I) for diagnosing OA.

MANAGEMENT OF WORK-RELATED ASTHMA

This guideline addresses management of WRA once it is diagnosed (Table 3). There are 11 studies incorporated into this analysis,[1,12,43,81,130–137] although none met high- or moderate-quality criteria. Thus, the panel reached the following conclusions regarding management of WRA on the basis of consensus.

Early diagnosis and early avoidance of further exposure, either by relocating the worker or substituting the hazard, offer the best chance of complete recovery. Patients with sensitizer-induced OA should be removed from further exposure to the causative agent in addition to providing other asthma management,[12] and it is recommended to educate all parties that complete avoidance of exposure to the identified antigen is preferred; however, complete removal is not always possible, for example, because of economic constraints of job change or loss, as well as patient preferences to continue in the same occupation. In that instance, the Panel recommends transfer to low levels of exposure to the asthmagen and frequent monitoring with questionnaire and spirometry surveillance to detect asthma deterioration. Reducing exposure to the causal agent in addition to providing immunotherapy and other asthma management, where applicable, depends on the asthmagen, level of exposure, severity of asthma (Table 4), and the clinical judgment of the physician. If disease progression is documented, then removal from the exposure is strongly recommended. An exception is isocyanate-induced OA. This requires removing the worker from exposure, as there have been reported deaths in patients on medication and using respiratory protection.[138–143] Studies have found that continued toluene diisocyanate exposure has been associated with increasingly persistent and severe respiratory symptoms.[137,144–146] Personal protective equipment is not recommended as the only treatment option for managing OA.

Very few studies have specifically examined pharmacologic treatment in the management of WRA. The pharmacologic treatment of OA and WEA does not differ from the treatment of asthma that is not work related[12]; it relies on a stepwise approach according to the severity of asthma and asthma control. Treatment for patients with a diagnosis of severe asthma has been recommended by the European Respiratory Society and the American Thoracic Society, but these recommendations did not exclude or specifically address OA or WEA.[147] The effectiveness of anti-asthma medications in patients who remain exposed to the causal agent has not been specifically addressed in previously published guidelines,[12,131] or in the Agency for Healthcare Research and Quality systematic review.[1]

SUMMARY

This is the first WRA guideline to be published that is based on IOM-compliant criteria including systematic literature reviews, literature grading, expert panel consensus, and peer-review.[24] It is designed to be a resource for primary care providers, occupational medicine specialists, and pulmonary/allergy specialists who diagnose and manage occupationally related asthma.

RESEARCH RECOMMENDATIONS

Research into primary and secondary prevention is indicated to reduce the incidence of WRA. Also recommended is investigation to improve diagnostic methodology leading to earlier detection of sensitizer-induced OA, before progression to permanent asthma, and preventing further cases of sensitizer-induced OA. Management with pharmacological treatment options should be studied to identify treatments specific to OA and WEA, and to more specifically evaluate pharmacotherapy for different agents, for example, HMW versus low molecular weight antigens.

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TABLE 4. Medical Removal Considerations

Workplace Exposure*	Low Severity OA†	Moderately Severe OA†	Severe OA†
Low	Remove worker or reduce exposure; frequent surveillance with symptom questionnaire and spirometry. Remove worker if progression of disease	Remove worker. Selectively consider low exposure, with monthly surveillance with symptom questionnaire and spirometry. Remove if progression	Remove worker
Medium	Remove worker or reduce exposure; frequent surveillance with symptom questionnaire and spirometry. Remove worker if progression of disease	Remove worker	Remove worker
High	Removal of worker best option as exposure predicts progression	Remove worker	Remove worker

OA, occupational asthma.

*Workplace exposure is defined as follows:

(1) Low exposure—when regular airborne exposure to the causative agent is not expected.

(2) Moderate exposure—when airborne exposures at or below the level of the occupational exposure limit (OEL) of the causative agent are expected.

(3) High exposure—when airborne exposures above the level of the OEL of the causative agent are expected.

(4) The OEL selected should be a recent, scientifically reviewed, widely used guideline designed for use by industrial hygienists in making decisions regarding safe levels of exposure to various chemical substances and physical agents found in the workplace, such as the American Conference of Governmental Industrial Hygienists Threshold Limit Values®.

†Asthma severity is defined as follows:

(1) Severe—having abnormal FEV_1 (<70%) and requiring use of high-dose inhaled corticosteroids and long-acting inhaled beta-agonists for symptom control.

(2) Moderately severe—having abnormal FEV_1 (<70%) and symptoms that are well-controlled with low dose inhaled corticosteroids and long-acting inhaled beta-agonists.

(3) Low severity—having normal FEV_1 and symptom control by as-needed beta-agonist rescue or with low-intensity controller treatment such as low-dose inhaled corticosteroids, leukotriene receptor antagonists, or cromoglycates.

APPLICABILITY AND IMPLEMENTATION ISSUES

The strengths of this guideline include the following: (1) comprehensive literature search; (2) a large database of studies from which to base recommendations; (3) the methodological literature abstraction and grading; and (4) the expert medical panel and expert external review processes. The main weaknesses stem from a general lack of high-quality diagnostic studies that are specific to WRA. Further rigorous study needs to be conducted in occupational settings for both diagnosis and management of WRA.

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