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OCCUPATIONAL AND
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Occupational/Work-Related Asthma

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Table of Contents

Summary of Recommendations	4
Introduction	5
Classification of Work-Related Asthma	6
Impact	7
Etiology.....	8
Other Airways-Associated Dysfunction Disorders.....	9
Diagnostic Approach	9
Symptoms and Signs	9
Complications and Comorbid Conditions Relevant to Work.....	9
Diagnostic Assessment of Work-Related Asthma	10
Medical History	11
Physical Examination.....	15
Diagnostic Recommendations.....	16
Spirometry.....	16
Peak Expiratory Flow Rates (PEFR).....	20
Nonspecific Bronchial Provocation Test.....	21
Specific Immunological Testing	24
Skin Prick Testing.....	27
Specific Inhalational Challenge Testing.....	29
Nitric Oxide (Fractional Exhaled Nitric Oxide, FENO).....	31
Nasal Lavage.....	32
Treatment Approach	34
Management of Irritant-Induced OA	34
Management of WEA	34
Management of Sensitizer-Induced OA	34
Prevention and Exposure Control	34
Treatment Recommendations	38
Removal or Reduction of Exposure	38
Pharmacologic Treatment.....	43
Immunotherapy for Sensitizer-Induced Asthma	46
Prognosis.....	48
Employment Outcome	48
Specialty Care	49
Medical Surveillance	49
Appendix 1: Low-quality/Supplementary Studies.....	51
References.....	51

Summary of Recommendations

The following table summarizes the recommendations from the Evidence-based Practice Asthma Panel for diagnostic testing and management of work-related asthma. The recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles when higher quality evidence was unavailable or inconsistent. **The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, prior testing or treatment, and contraindications that are elaborated in more detail for each test or treatment in the body of this *Guideline* in using these recommendations in clinical practice or medical management.** These recommendations are not simple “yes/no” criteria, and the evidence supporting them is in nearly all circumstances developed from typical patients, not unusual situations or exceptions.

Recommendations are made under the following categories:

- Strongly Recommended, “A” Level
- Moderately Recommended, “B” Level
- Recommended, “C” Level
- Insufficient-Recommended (Consensus-based), “I” Level
- Insufficient-No Recommendation (Consensus-based), “I” Level
- Insufficient-Not Recommended (Consensus-based), “I” Level
- Not Recommended, “C” Level
- Moderately Not Recommended, “B” Level
- Strongly Not Recommended, “A” Level

Diagnostic/Treatment Intervention	Details	Recommendation
Bronchial Provocation	Mannitol Bronchial Provocation Test	Recommended, Evidence (C)
	Nonspecific Bronchial Provocation Test	Moderately Recommended, Evidence (B)
	Nonspecific Bronchial Provocation Test When Clinical History Is Compelling	Strongly Recommended, Evidence (A)
Exhaled NO	Exhaled Nitric Oxide Testing for Diagnosis of Occupational Asthma	Not Recommended, Insufficient Evidence (I)
	Exhaled Nitric Oxide Testing When More Objective Evidence is Needed	Recommended, Evidence (C)
	Exhaled Nitric Oxide Testing for Selective Monitoring of Asthma	Moderately Recommended, Evidence (B)
Immunological Testing	IgE-Specific Immunological Testing for High-Molecular-Weight Specific Antigens	Strongly Recommended, Evidence (A)
	IgE-Specific Immunological Testing for Low-Molecular-Weight Specific Antigens	Not Recommended, Insufficient Evidence (I)
	IgG-Specific Immunological Testing for High-Molecular-Weight Specific Antigens	Not Recommended, Evidence (C)
Inhalational Challenge	Specific Inhalational Challenge Testing	Recommended, Evidence (C)
Management	Anti-asthma Medications as an Alternative to Environmental Interventions	Not Recommended, Insufficient Evidence (I)
	Avoidance of Exposure	Recommended, Insufficient Evidence (I)
	Education on the Persistence of Exposure	Recommended, Insufficient Evidence (I)
	Immunotherapy for the Management of Sensitizer-Induced Asthma	Recommended, Evidence (C)

Diagnostic/Treatment Intervention	Details	Recommendation
	Inhaled Corticosteroids	Recommended, Evidence (C)
	Pharmacological Treatment Strategies	Recommended, Evidence (C)
	Respiratory Protective Devices (severe asthma or moderately severe asthma in worksites with medium or high exposures)	Not Recommended, Insufficient Evidence (I)
	Respiratory Protective Devices (stand-alone intervention, mild, moderate severity)	Not Recommended, Insufficient Evidence (I)
	Reduction of Exposure for the Management of Irritant-Induced Asthma	Recommended, Insufficient Evidence (I)
	Reduction of Exposure for the Management of Sensitizer-Induced Asthma	Not Recommended, Insufficient Evidence (I) (see full recommendation for details)
	Reduction of Exposure to Low-Molecular-Weight Asthmagens for the Management of Sensitizer-Induced Asthma	Not Recommended, Insufficient Evidence (I)
Nasal Lavage	Nasal Lavage Fluid Testing for Diagnosis of Occupational Asthma	Not Recommended, Insufficient Evidence (I)
	Nasal Lavage Fluid Testing for Specific Allergen Testing and Monitoring of Symptomatic Workers	Recommended, Evidence (C)
PEFR	Peak Expiratory Flow Rates – Serial Measures	Moderately Recommended, Evidence (B)
Skin Prick Testing	Skin Prick Testing for High-Molecular-Weight Allergens	Strongly Recommended, Evidence (A)
	Skin Prick Testing for Low-Molecular-Weight Allergens	Moderately Recommended, Evidence (B)
	Skin Prick Testing for Other Allergens Not Covered Above	Not Recommended, Insufficient Evidence (I)
Spirometry	Spirometry	Recommended, Insufficient Evidence (I)

Introduction

Work-related asthma (WRA) presents with symptoms of asthma that began or became worse at work, usually in the context of exposure to a new chemical or environmental change. The symptoms may occur during or after work hours. The specific respiratory symptoms in WRA patients are the same as in non-WRA patients, which requires a high level of suspicion and incorporation of work history in the evaluation of all cases of adult-onset asthma. They include cough, wheeze, shortness of breath, and chest tightness, with physiological evidence of reversible/variable airway obstruction and/or hyperresponsiveness.^[3, 6, 7]

Occupational asthma (OA) is defined as new-onset asthma in the workplace and can be caused by exposure to either a workplace sensitizer or an irritant. OA is further classified into OA with latency or OA without latency. OA without latency is less common and is believed to represent from 5 to 15% of all OA cases.^[1] OA with latency is observed in all instances of immunologically-mediated asthma. The latency period, which represents the time between the first exposure and the development of symptoms, can vary from weeks to years. It reflects the time for induction of an immunological response to the workplace allergen. OA without latency can occur after a single exposure to irritant gas, fumes, or chemicals, such as nitrogen oxide, ammonia, and chloride.^[1, 18] This was originally classified as reactive airways dysfunction syndrome (RADS).^[18] RADS is an overused diagnosis and should be reserved for new-onset reactive airways associated with a single incident. It classically relies on a single high-level (non-routine) exposure to an inhaled irritant.

Brooks and other authors have suggested modification of these criteria to include a role for multiple cumulative irritant insults, or even for an allergic diathesis along with the irritant exposure that would result in new-onset workplace asthma involving latency. Low-level irritant-induced OA with latency may be difficult to distinguish clinically from sensitization-induced asthma.^[19] However, clear-cut guidelines beyond Brooks 1985 have not been established for such irritant-induced asthma.^[20, 21]

Work-exacerbated asthma (WEA) is defined as “preexisting or concurrent asthma that is worsened by workplace conditions;” the activation of preexistent asthma or bronchia hyper-responsiveness may occur due to many factors such as temperature, exercise, dust, or low-level irritants.^[17, 22]

In summary, irritant-induced asthma includes (a) RADS, which develops after a single episode of high-level exposure or (b) irritant-induced asthma with a “not so sudden” onset, which occurs after a single exposure or repetitive episodes of exposures. The “not so sudden” cases often, but not always, have a history of pre-existing asthma that was in remission at the time of exposure. WEA occurs when an individual with pre-existing/concurrent asthma develops a worsening condition due to exposures specific to the workplace.

Classification of Work-Related Asthma

Occupational/work-related asthma may be classified as follows:

1. Exacerbation of pre-existing asthma (WEA)
 - a. Irritant gases
 - b. Allergens
 - c. Other (e.g., environmental tobacco smoke, exercise, other irritants)
2. New-onset asthma
 - a. Without sensitization
 - i. Endotoxin (Byssinosis from cotton dust)¹
 - ii. Cholinesterase inhibitors (pesticide exposure)
 - iii. Inflammatory response (chlorine, ammonia)
 - iv. Irritant induced:
 1. Acute irritant exposure (RADS)
 2. Low-level irritant exposure with latency)²
 3. Cold-induced (nonspecific)
 4. Nonspecific
 - b. With sensitization

¹In the early stage when there is reversible airflow constriction and before it becomes a fixed obstruction.

²New-onset asthma due to low-level irritant exposure has been described but is not widely accepted in the absence of pre-existing airway hyperreactivity.

- i. High-molecular-weight compounds: IgE-mediated (complete allergens: animal, plant, bacterial)
- ii. Low-molecular-weight compounds
 - 1. IgE-mediated (platinum, antibiotics)
 - 2. Uncertain mechanism (isocyanates, amines, acid anhydrides, plicatic acid)

Table 1. Types of Work-related Asthma

Nomenclature	Term	Defining Features
Sensitizer-induced occupational asthma (OA)	Occupational asthma with latency of allergic or presumed immunological mechanism (not necessarily IgE)	Immunological/hypersensitivity component and diagnostic tests include measures of specific sensitization (e.g. skin prick test, serum specific IgE, circulating IgC against the antigen or skin sensitization).
Irritant-induced occupational asthma (OA)	Occupational asthma without latency	No allergic component and worker is not “sensitized” to an agent. Rather, the agent causes inflammatory responses through irritant mechanisms.
Work-exacerbated or work-aggravated asthma (WEA)	Work-exacerbated 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 (e.g. cold, exercise, non-sensitizing dust, fumes, or sprays) that provokes an asthmatic reaction.

Adapted from the American College of Chest Physicians (ACCP).

More than 200 agents have been reported to cause WRA, based on epidemiological and/or clinical evidence. Many occupations and exposures have been associated with allergic OA. Asthmagens (sensitizing antigens resulting in asthma) are often classified into categories based on their molecular weight, with high molecular weight defined as $\geq 5,000$ daltons versus low molecular weight as $< 5,000$ daltons. Molecular weights are believed to be important in the mechanisms of action in the development of OA.^[1] A list of common occupations and exposures was provided by Malo and Chan-Yeung.^[23]

Prevalence estimates of asthma and WRA have been assessed in small cohort and cross-sectional studies. Studies of workplaces with exposures to specific substances reported prevalences of asthma or OA ranging from 3% to 54%.^[1, 2, 24, 25]

The predisposing factors for developing WRA are not well known. Atopy is the primary established risk factor for OA, operating largely with respect to high-molecular-weight antigens such as animal proteins. It has been proposed that human leukocyte antigen class-2 (HLA class II) alleles can be a risk factor for the development of WRA resulting from low-molecular weight agents.^[12, 26, 27] However, HLA typing is not routinely performed for asthma clinically and has no demonstrated value in individual diagnosis.

Medical management and compensation decisions require a thorough assessment of suspected OA. OA may be mistaken for non-occupational asthma unless a detailed history, including occupational history, and appropriate medical tests are performed to support an association with work.^[28]

Impact

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.^[1-5] Increased airway responsiveness to a variety of stimuli is typical. Work-related asthma (WRA) includes both occupational asthma (OA, asthma of occupational origin) and work-exacerbated asthma (WEA). OA includes sensitizer-induced asthma, resulting from sensitization to an antigen in the workplace, and irritant-induced asthma, resulting from reactive airways disease, which has been provoked by workplace exposures to irritants. Each has the potential for considerable acute morbidity, long-term disability, and adverse social and economic impacts.^[6-12]

Work-related asthma has become the most common form of occupational lung disease in many industrialized countries, with approximately 10 to 15% of all prevalent cases of adult asthma attributed to occupational factors.^[6-9, 11, 13, 14] The percentage of new-onset adult asthma attributable to occupational causes is considered to be much higher, up to a third of all cases.^[15, 16] The frequency of WEA, defined as preexisting reactive airways disease that is made temporarily or permanently worse due to occupational exposures, is known to be much higher than new-onset OA.^[17]

The diagnosis of WRA is a specialty-level function and is usually done by physicians who have special training and expertise in occupational lung disease and workplace exposures. If the treating physician does not have this specialized expertise, prompt referral is advised.

Etiology

More than 300 natural and synthetic chemicals have been implicated in causing WRA. This section highlights a few commonly encountered chemicals causing “asthma with latency” (a term that suggests a process that does not provoke a response on first contact, which implies that sensitization may be the mechanism) that are seen in the occupational setting. More extensive lists of agents and occupations are available (e.g., Malo and Chan-Yeung 2009: [http://www.jacionline.org/article/S0091-6749\(08\)01671-0/pdf](http://www.jacionline.org/article/S0091-6749(08)01671-0/pdf); Toxnet: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>; Centers for Disease Control and Prevention: <http://www.cdc.gov/niosh/topics/>; Agency for Toxic Substances and Disease Registry: <http://www.atsdr.cdc.gov/>; and Haz-Map: <https://haz-map.com>).^[23, 29-32]

When referring to etiologic chemicals, these substances are often divided between high-molecular-weight (HMW) and low-molecular-weight (LMW) agents. The former group includes proteins and polysaccharides of plant or animal origin (>5-10 kD), whereas the latter group comprises low-molecular-weight chemicals (e.g., isocyanates, trimellitic anhydride, formaldehyde). This distinction is used to draw attention to typical mechanisms of pathogenesis. In particular, HMW agents can serve as direct sensitizing antigens, leading to classic IgE-mediated immune response. LMW compounds act as haptens, binding to existing proteins in the body and producing an IgE response. These mechanisms lead to asthma after a latency period. Typical HMW IgE-mediated examples would be flour or laboratory animal proteins, while acid anhydrides and metals would be LMW examples.

However, there are LMW antigens that cause asthma without an IgE mechanism being currently identified. Immune mediation is thought to exist as the patients still present with a latency period. Examples include the di-isocyanates – toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI) – and formaldehyde and cleaning agents. Even with immunologic mechanisms present, there may be non-immune pathways operating. This has been seen with TDI as well as Western Red Cedar due to the latter containing plicatic acid.

Specific HMW Chemicals:

- Grains and flours, in particular wheat and soya, have been among the most commonly described products. This is due not only to the flour product itself, but at times due to bug infestation into the material as well as additives including enzymes. Bakers and food processors would be a risk group, as well as dock workers exposed to shipping of the materials.
- Animal proteins are HMW asthma precipitants that come from dander, fur, hair, saliva, or urine. Animal urine protein is probably the most potent immunizing source in this group. Workers at risk for this would include farmers, veterinarians, and laboratory researchers or their assistants.
- Much attention has focused on the HMW latex exposure. This natural product (derived from the rubber tree) not only causes WRA, but also contact dermatitis. This latter condition is seen most commonly in health care workers. Environmental control in the form of avoiding latex gloves has helped diminish the burden of this condition.

Specific LMW Chemicals:

- Acid anhydrides are a large group of LMW compounds including phthalic anhydride, trimellitic anhydride, maleic anhydride, and tetrachlorophthalic anhydride. Products manufactured include plastics, dyes, adhesives, and resins, with workers involved in production being at risk for WRA. Exposed workers with a history of cigarette use are at particular risk.
- Platinum salts and aluminum can produce symptoms in workers exposed in jewelry and alloy production. Exposed workers with a history of cigarettes are at particular risk.

- Di-isocyanates have been identified as the most common cause of LMW WRA. The commonly used di-isocyanates in industries are TDI, MDI, hexamethylene di-isocyanate (HDI), and prepolymers of MDI and HDI. They all have in common N=C=O groups that are highly reactive and explain their sensitizing properties. The reported prevalence of di-isocyanate induced asthma has varied but may have been reduced in recent years due to better preventive measures.^[33] These chemicals have properties to form polymers giving rise to polyurethane. They are used across a wide variety of industries in the production of flexible and rigid foam, binders, coatings, elastomers, and paints.

Other Airways-Associated Dysfunction Disorders

Although asthma is the principal occupational airways disorder in working adults, other conditions should be considered as part of the differential diagnosis. These may include fixed airway obstruction, upper airway abnormalities, laryngeal disorders, and cardiac diseases.

These specific respiratory disorders should be considered in the differential diagnosis:

- Asthmatic bronchitis: This is an inflammatory disorder of airways that can have a hypersensitivity or an irritant component or both; bronchiectasis may also be present.
- Hypersensitivity pneumonitis: Predominantly an interstitial disease, HP often has an airways component, especially acutely.
- Chronic obstructive pulmonary disease (COPD): This disorder is characterized by a fixed obstruction to airflow with or without a reversible component. It may be associated with smoking and manifested by emphysema or bronchitis,^[34] or dust (such as silica, coal, or asbestos) exposure.^[35]
- Allergic rhinitis and atopy: Persons with allergies often experience wheezing and reversible airflow obstruction during exacerbations of their allergies as a secondary symptom, especially during acute allergic reactions and respiratory tract infections.
- Bronchiolitis and other obstructive airways diseases in adults, such as constrictive bronchiolitis and during progression to bronchiolitis obliterans.
- Eosinophilic pneumonias: A family of disorders presenting as asthma but characterized by a hyperimmune response involving eosinophils. This family includes allergic bronchopulmonary aspergillosis (ABPA) and Loeffler's disease.
- Upper airway obstruction in adults may be confused with asthma and stridor may be confused with wheezing. Acute upper airway obstruction, such as that occurring with epiglottitis and anaphylaxis, is a medical emergency and is unlikely to be confused with asthma. Chronic partial upper airway obstruction may be seen in tumors, sarcoidosis, vocal cord paralysis, vocal cord papilloma and a variety of rare conditions (e.g., retropharyngeal abscess) unlikely to be confusing in practice.^[36]

Diagnostic Approach

Symptoms and Signs

Asthma is primarily a disease of airway inflammation and reactivity. The cardinal symptoms of asthma are episodic shortness of breath, wheezing, and cough; in comparison, the predominant symptoms of bronchitis are cough and sputum production.^[37]

Cough requires special attention. It has been found to be the single most troublesome complaint for patients with stable, chronic asthma, which may also be true for other airway conditions.^[38] Many cases of asthma do not show wheezing and have cough as the predominant symptom,^[39] as do most cases of bronchiolitis.

Complications and Comorbid Conditions Relevant to Work

Asthma may present in complex ways with a variety of secondary symptoms and problems that affect daily life and work. For example, asthma may trigger chronic cough and secondary hoarseness that indirectly interferes with some jobs (e.g., voice changes, or the inability to carry on a conversation). Gastroesophageal reflux disease (GERD) is often associated with asthma, may be triggered by the effect of bronchodilator medications on the lower

esophageal sphincter, and may make asthma symptoms worse. Vocal cord dysfunction is distinct from asthma but may often coexist with it, or it may be triggered by GERD or exposure to irritants.

Such secondary conditions may also affect fitness for duty, work capacity, and job performance.^[40] For example, complications may affect speech and voice, alertness and cognitive acuity, and risk for sleep apnea, and should be considered in assessing fitness for duty and in impairment evaluation. Although these complicating symptoms do not necessarily change with improvement in asthma status or asthma treatment, they frequently require secondary diagnosis and treatment in order to return the individual to work.

- *Coughing spells.* These may be disruptive in the workplace and are sometimes associated with acute rhinitis and susceptibility to fragrances and capsaicin.
- *Voice changes and unreliability.* There are many reasons why asthma affects the voice: breathlessness, vocal cord edema due to inhaled corticosteroids, concurrent allergies, and “paradoxical vocal fold motion dysfunction” (VCD). VCD also occurs in other respiratory conditions, but is more common in asthma.^[41-43] Patients with asthma and similar airway problems may have difficulty in any job requiring them to use their voice to communicate.
- *Irritability, loss of concentration, and restlessness.* This may be due to distraction, given that cough, mild choking sensations, and breathing issues interfere with close concentration and fine work.
- *Musculoskeletal symptoms.* Chronic coughing and altered trunk mechanics may be associated with chest (thoracic cage) pain and low back pain.
- *Leg pain.* Some asthma medications (including formoterol) may cause restless leg syndrome or alter tissue levels of potassium, magnesium, and other elements that can cause muscle cramps.
- *Eye problems.* Abnormalities in the stability of tear film may accompany nasal inflammation and airways disorders.^[44] Cough and increased intrathoracic pressure may raise pressure levels in the eye, causing small blood vessels to become engorged and even to break.
- *Sleep disorders, fatigue, and cognitive deficits.* These connected conditions are associated with night-time asthma and disturbed sleep patterns, not just time awake at night due to wheezing, shortness of breath, leg pain, and especially cough. The result is a substantial decrease in performance in any task requiring mental processing, short-term memory, and sustained attention, even when asthma is treated.^[45, 46] There has long been strong evidence that RADS also affects the upper airway.^[47] It may occur as obstructive sleep apnea because of dysfunction of the upper airway – a feature of reactive upper-airways dysfunction syndrome (RUDS) – or it may reflect reactive airways and cough during the night. The relationship between obstructive and central (brain-driven) sleep apnea also appears to be closer than has been previously believed and predominantly central apnea may account for some cases. Further, sleep apnea itself, apart from obesity, with which it is confounded, substantially raises the risk of a variety of serious complications, including heart attacks and stroke.^[48]
- *Depression.* This is common to all chronic diseases and is known to occur in asthma. Sleep deprivation may aggravate it in asthma and bronchitis.^[49]
- *Gastro-esophageal reflux disease.* GERD often coexists with asthma and may be associated with it, although both diseases are also common alone.^[50] GERD, phlegm-producing cough, and a heightened cough reflex may predispose the patient with asthma to choking and gagging.^[51, 52]

These symptoms and signs cluster in five sets of related conditions, which have been given broad rubrics of *panic-fear*, *airways obstruction*, *hyperventilation*, *fatigue*, and *irritability*. Within these categories, symptoms and signs tend to track one another; that is, within a cluster, symptoms have been observed to appear together rather than separately.^[53]

Diagnostic Assessment of Work-Related Asthma

In this guideline, we emphasize pulmonary evidence-based evaluations. See the [General Approach to Initial Assessment and Documentation](#) guideline for an overview of occupational evaluations, including the history and physical examination. More specialized pulmonary history and diagnostic history is required for a diagnosis of WRA. The American College of Chest Physicians published the following criteria in 1995 for establishing a diagnosis of WRA, all of which are required:

- a history compatible with work-related asthma;
- presence of airflow limitation and its reversibility;

- in the absences of airflow limitation, the presence of nonspecific airway hyperresponsiveness; and
- demonstration of work-relatedness of asthma by objective means.^[9]

Algorithm 1 is a consensus-based recommendation from the Evidence-based Practice Asthma Panel for the diagnostic evaluation of an individual with suspected work-related asthma.

Medical History

Taking a thorough medical history is the first step when suspecting occupational lung disease. The history should include three components: 1) current and previous respiratory symptoms; 2) an occupational history that includes a detailed exposure history; and 3) focused questions linking the symptoms to the workplace, in space, time, and latency from first exposure. The ultimate goals of a structured investigation are to assist in determining causation, implementing treatment, and intervening to prevent disease in other exposed workers.^[54]

The patient should be queried regarding childhood respiratory symptoms, as well as colds, bronchitis, pneumonia, hay fever, sinus problems or allergies. Evidence for atopic disease should be sought (e.g., asthma, hay fever, and eczema).^[55] Ask about the length and severity of these illnesses, medication history, and whether emergency department treatment or hospitalization was required. Some studies show that atopy increases the risk of WRA or sensitization for certain asthmagens including enzymes, isocyanates, animals, bakery allergens, dyes, green coffee, castor bean, certain shellfish, and acid anhydrides.^[56] While family history is important in asthma incidence, the same family history does not reliably predict occupational lung disease in exposed workers.^[57]

A history of asthma symptoms arising during a period of employment, especially with improvement on the weekends or holidays, is suggestive of WRA. However, more evidence is needed to verify that the symptoms are due to asthma, and that the asthma is related to workplace exposures.^[28]

Although the probability of WRA from history alone is not high, a typical history consistent with WRA can lead to a pretest probability as high as 70% before diagnostic tests are conducted.^[7] Cote et al. reported that a history suggestive of western red cedar asthma had a diagnostic specificity of 45%.^[58] In contrast, Malo et al., reported that 76% of referred clinical patients reported improvement in respiratory symptoms while away from work but were subsequently found to have no objective evidence of WRA.^[54] Taken together, the clinical history is believed to be more reliable for excluding than confirming the diagnosis of WRA.^[9] For OA without latency, frequently resulting from accidents or other non-routine workplace conditions, the history is often the primary source of information to establish that a highly offensive atmosphere was present. In this section, we will use the words inflammatory or irritating interchangeably.

Medical History Questionnaire

Larger employers often have the benefit of workplace surveillance programs, medical staff on location, accessible spirometry, and general knowledge of the chemicals used in the work environment. This may allow a more focused history than the general recommendations below. Symptoms of work-related asthma include episodic wheezing, chest tightness, cough, dyspnea, or recurrent attacks of bronchitis with cough and sputum production. The history³ should include the following questions:

1. What are your symptoms?

- What are your symptoms of concern? Do you have cough, shortness of breath, or wheezing?
- When did these symptoms first occur? Was there an event that precipitated the symptoms?
- When did these symptoms first occur relative to the beginning of your work in that location?
- How frequently have symptoms occurred?
- Do they get worse at any particular time of day or night?
- If yes, indicate below the patterns of the symptoms:
 - Do these symptoms ever begin immediately after starting work (less than 1 hour)?

³History for asthma does not replace the OSHA questionnaire when required by regulations. See OSHA Respiratory Questionnaire Appendix C to Sec. 1910.134: OSHA Respirator Medical Evaluation Questionnaire.

- Do these symptoms begin hours after starting work?
- Do these symptoms continue or start while at home?
- Do they improve when you are away from work such as on weekends, nighttime (off-shift) or holidays or vacations?
- Are your symptoms constant or intermittent? What makes them worse or better?
- Has the pattern of your symptoms changed over time? How?
- Is there a seasonal pattern to your symptoms? What time of year are they the worst?
- Are the symptoms associated with any substance or process at work?
- How frequent and severe are your symptoms? Have your pulmonary symptoms included throat tightness, difficulty with inspiration or expiration, harsh sounds, cough, or sputum production?
- Did any emergency room or physician visit document lung function?
- Do you have a history of pre-existing asthma (particularly childhood asthma, which can recur in adults), including prior frequency of symptoms, treatment with asthma medication, and response to medications?
- Do you have a history of allergy or has anyone mentioned the word atopy to you?
- Do you have symptoms of allergic rhinitis and/or conjunctivitis that are worse with work?
 - Did the symptoms begin after a one-time, high-level workplace inhalation exposure to an irritant gas, fume, smoke, or vapor?
- How does medication use affect the symptoms? Do you use prescribed medications, over-the-counter medications, and/or complementary/alternative preparations? Do you use pulmonary and non-pulmonary medications? Are you taking an angiotensin-converting enzyme inhibitor or beta-blocker?
 - Do others at work have the same symptoms you have?

2. How did your condition develop?

PAST:

- Have you had previous similar episodes before your current job?
- What kind of treatment did you receive for these symptoms in the past?
- Who was your physician?
- Were the treatments effective?

CAUSE:

- What do you think caused the problem?
- How do you think it is related to work?

OCCUPATIONS AND ACTIVITIES:

- What do you do for work?
- Current occupation and specific work activities including shift, hours, duration, and days worked per week. (Patients working 6 days a week or more may not have enough time away from work to symptomatically improve.)
- Any past work history including specific activities, especially if there is a history of similar symptoms?
- What chemicals or substances including gas, fumes, vapors, dusts, or aerosols do you work with? What about at home?
- What is the work area's room size, specific ventilation, other co-worker reports, exhaust hoods, remodeling, and recent change in processes? Are there Material Safety Data Sheets (MSDSs) and industrial hygiene reports available?
- Were there changes in work processes in the period preceding the onset of symptoms? Symptoms of asthma that develop or worsen after a worker starts a new job or after new materials are introduced on a job are suggestive. (A substantial period – from months to years – can elapse between initial exposure and development of symptoms.)
- Was there an unusual work exposure before the onset of initial asthma symptoms?

- Do you have any protective equipment at work, such as masks or respirators? How often do you use them? Are they required?
- Do you have a second job (moonlighting)?

NON-OCCUPATIONAL ACTIVITIES:

- What is your home environment, including any hobbies, crafts, pets, family members who work with chemicals, family members who smoke, living near an industrial plant, or living near congested traffic area?^[59]
- What are your leisure activities (e.g., woodworking, gardening, welding)?

3. How do these symptoms limit you?

- Are there any activities that you can no longer perform?
- Do you feel more short of breath during exercise?
- Do you feel more short of breath when doing normal daily activities?
- How long have your activities been limited?

4. Do you have other medical problems?

- Do you have headaches, fatigue, malaise, weight loss, appetite changes, fever, physical inabilities, or exercise intolerance?
- Do you have any autoimmune, infectious, or metabolic diseases?
- Do you have any allergies?
- Do you have any other respiratory diseases or conditions?
- Do you smoke? Does someone else in your environment smoke?
- Do you use other drugs, including marijuana?
- Do you have diabetes or HIV?
- Have you ever had cancer?

5. What are your expectations regarding your return to work and disability from this health problem?

6. What are your concerns about the potential for further injury to your lungs?

7. How do you like your job, your supervisor, and co-workers? What is your relationship with your co-workers and supervisor and how do they treat you?

8. What do you hope to accomplish during this visit?^[13]

Standardized Questionnaires

There have been general articles and questionnaires used to document occupational illness.^[60, 61]

Similarly, authors have suggested questions targeting work-related pulmonary conditions.^[62, 63]

Questionnaire adequacy measures have shown instruments that are reliable, valid, and correlate with testing.^[64-68] Reliability should be considered as reproducibility of response and validity is a measure of how well the instrument measures the intended target. Ultimately, there have been investigations looking at correlations between history and diagnosis of occupational lung disease.^[69] Malo et al. examined the accuracy of the medical history in 162 workers referred for evaluation of OA, using specific inhalation challenge to confirm the diagnosis. They reported a positive predictive value of 46% and negative predictive value of 83%. In a study by Baur et al., who used methacholine testing and specific bronchoprovocation challenge, the predictive value of the medical history was 90% with a negative history and 30% with a positive history. Vandenplas et al. reported a specificity of 14% and sensitivity of 87% in natural latex workers when compared to specific inhalational challenge testing for diagnosis of OA.^[70]

All instruments have limitations that will miss true cases of work-related asthma.^[54, 71] The American Thoracic Society Division of Lung Diseases (ATS-DLD) instrument^[72] is the most widely used questionnaire for pulmonary symptoms and disease that is validated in the literature.

Family History

A family history of atopic diseases may help identify individuals with greater susceptibility to OA with latency, particularly for OA to high-molecular-weight agents. However, it is important to note that many workers with OA will have no family history of atopy, and conversely, many workers have an atopic history without OA. A history of similar symptoms in other household and family members may also help identify non-occupational causes of asthma, such as home and hobby exposures.

Occupational History

The physician should obtain an accurate and detailed history of current and prior occupations. All possible occupational exposures should be identified, especially those that are known to induce airflow obstruction (e.g., animal and plant proteins, organic dusts, proteolytic enzymes, specific chemicals such as isocyanates and anhydrides, noxious fumes, metals, and drugs). Both routine and episodic tasks are potential exposures and should be evaluated.

The physician should also attempt to quantify the exposure. The intensity (duration and concentration), frequency, duration, and peak concentrations of the exposures are all important to document if possible.^[73] A detailed history of current exposure status is important. Lam et al. reported a significant improvement in spirometry results at a mean of 0.8 years after patients with OA were removed from exposure.^[74]

Exposure Assessment

Respiratory injury is dependent upon both the site of toxin deposition and the type of cell and structure damaged. The concentration and chemical properties (pH, water solubility, reactivity) of the substance involved are relevant, as they affect the site of deposition. The degree to which a given inhalational exposure results in disease not only reflects the intensity, duration, and type of exposure, but also varies based on host factors such as genetic susceptibility, comorbid conditions, and lifestyle factors and habits (e.g., cigarette smoking). The presence of work-related pulmonary conditions should include assessment of whether representative measurable environmental determinations exist, to ascertain whether there has been sufficient exposure to affect the lungs.^[75] However, measurable environmental determinations are not routinely performed in most workplaces, and when performed, represent a brief snapshot of selected exposures that may or may not reflect the relevant work exposures.

Information on work exposures may be obtained from MSDSs, industrial hygiene data, employer records, and union health and safety personnel information.^[9] In general, at least one source of objective information is needed for evaluation of cases of suspected work-related asthma. The MSDS is usually the initial source of information; however, sensitizing ingredients in low concentrations may not be listed, so identifying them may require a phone call to the technical staff of the manufacturer. Published literature may also be helpful.^[76]

It is important to establish the following:

- All known exposures in any environment to any chemicals or substances including gas, fumes, vapors, dusts, and aerosols, particularly known or suspected asthmagens.
- Workplace history of room size, ventilation, current and past use of personal protective equipment (PPE), other co-worker reports, exhaust hoods, remodeling, recent change in processes, and industrial hygiene reports (if available).
- MSDSs should be reviewed, if available, for both health effects information and PPE recommendations by the manufacturer of materials used.

For exposure assessment, the standards and methods of evaluation widely used are those promulgated by the American Conference of Governmental Industrial Hygienists (<http://www.acgih.org>). In particular, the group's biological exposure indices and threshold limit values are more frequently evaluated and updated than those occupational exposure levels (OELs) from the Occupational Safety and Health Administration (OSHA), the Mine Safety and Health Administration (MSHA), and the permissible exposure limits (PELs) defined by the National Institute for Occupational Safety and Health (NIOSH). OELs are set primarily to provide a means for standardized

hazard assessment of a material, communicate a relatively safe target concentration relative to time interval that can be verified quantitatively, and to provide a target control approach to ensure that workers are not overexposed.

For workplace risk assessment, the *NIOSH Pocket Guide to Chemical Hazards* [77] provides a concise summary of toxicologic information. Most inhaled particles with a diameter of greater than 3 µm are deposited along the airways of the upper and lower respiratory tract. Smaller particles may penetrate the alveolar region, but the physical characteristics, total mass and chemistry of the particle and airway structure and airflow must be considered.^[78] Water-soluble gases, vapors, and aerosols are usually deposited in the upper airway, while water-insoluble substances affect the lower airways or lung parenchyma. Extremes of pH also are associated with severity of injury. Of importance in evaluation of respirable exposures is the distance of the worker from the source. The area tested should usually be within 2 feet of the worker's mouth and nose.^[79] The probability of exposure is evaluated by considering the following: 1) the presence, form, and biological availability of potential hazards; 2) confounding exposure factors in the workplace or the patient's medical and occupational history that may account for other exposure potential and experience; 3) non-worker controlled factors such as materials used, ventilation, hazard control, and physical barriers; 4) the worker's use of employer-selected PPE (i.e., respirators, gloves) and training in appropriate work practices; and 5) the presence or absence of illness in co-workers with similar exposure potential.^[80]

Environmental History

Exposures outside the workplace are also important to evaluate and document. Patients should be queried regarding primary place of residence, its age, location, type, remodeling history, heating, ventilation, flooring, and past water damage. Hobbies such as automobile repair, woodworking, photography, ceramics, and gardening may expose individuals to agents that can cause or exacerbate asthma. The majority of the U.S. population is skin-test-positive to at least one environmental allergen.^[81] It is difficult to determine the relative contribution of work-related and non-work-related factors to the genesis of symptoms in people with multiple risk factors or exposures.

Smoking History

The greatest threat to personal lung health is from tobacco inhalation.^[5, 82] Although it is customary to quantify tobacco use in terms of pack-years, the variation in cigarette type and inhalational habits does not permit more than an approximation for potential lung injury.^[83] Cigarette smoking is a recognized risk factor for common airway diseases with the unusual exception of diisocyanate asthma.^[56] The smoking history should quantify the packs per day and the years smoked. Cigarette smoking may have an additive effect to airways obstruction from other causes, it may superimpose additional symptoms, or it may lead to misdiagnosis if the condition is apportioned disproportionately to smoking. Cigarette smoking may condition or modify the response to some antigens, but this is not known at this time and cannot be assumed.^[9, 55] Regardless of the history, a physical examination and diagnostic testing should be conducted as indicated.

Physical Examination

The art of physical examination traces its modern roots to the introduction of the stethoscope by Laennec in 1821. Standard textbooks provide guidance on pulmonary examination.^[84, 85] In general, an occupational pulmonary physical examination should include elements of the following:

- Inspection for stigmata of pulmonary disease as well as potential etiologies including mucous membrane abnormalities, nasal polyps/swelling, clubbing, nasal flaring, nasal crease line, accessory muscle use, AP diameter
- Palpation primarily for chest wall abnormalities, tracheal deviation, or tactile fremitus
- Percussion for resonance to identify aeration, diaphragm level, suggestion for fluid interface, or consolidation
- Auscultation for inspiration-to-expiration ratio and breath sounds including crackles, wheeze, and bronchi
- Cardiac examination
- Dermal examination.^[86]

However, a shift has occurred in medicine where physical diagnosis is often measured against a technologic gold standard for the presence or absence of disease. Thus, a useful measure of an examination would be the likelihood of a finding causing a change in the probability of a disease. Numerically, the likelihood ratio is equal to the probability of a finding in patients with a disease over the probability of a finding in patients without a disease. For example, it is often taught that the crackles of fibrosis are late and fine, whereas those of COPD are early and

coarse. Yet, this assumption has never been rigorously tested. However, diagnostic pneumonia findings have been subjected to numerous studies and are incorporated in both diagnosis and prognosis.^[87-89]

Formal spirometry testing and interpretation is covered elsewhere. Many clinicians will use simple clinical tests as part of their “physical examination.” This includes obtaining a simple pulse oximetry reading and/or having the patient walk in the hallway to identify desaturation.

Diagnostic Recommendations

Spirometry

Spirometry testing is an essential component in the evaluation and management of persons with possible work-related asthma.^[90-96] Spirometry with or without bronchodilator administration has four distinct potential roles when WRA is a concern:

- Determining whether asthma is present
- Excluding other “asthma-like” conditions
- If asthma is present, helping to inform the conclusion about whether the asthma is work related
- Monitoring response to therapy (and possible return to work)

Spirometry for Diagnosing Work-Related Asthma

Spirometry is recommended as an initial evaluation method for diagnosing work-related asthma.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Rationale for Recommendation

Indications for spirometry with or without bronchodilator for the evaluation of work-related asthma include signs and symptoms associated with a history consistent with work-related asthma (e.g., a worker experiencing chronic or intermittent cough, chest tightness, wheezing or dyspnea, occurring at the workplace or developing over several hours following the end of a work shift or awakening from sleep, which may or may not be obviously associated with the same location, product, process, or activity, or change in asthma medication use pattern).^[90, 97-99]

Spirometry with bronchodilator is an essential test for the evaluation of pulmonary function and would be performed in most cases whether or not WRA is under consideration. Evidence for the utility of spirometric testing in the diagnosis and management of general asthma is summarized in other evidence-based guidelines.^[99, 100]

Spirometry is also included in other more specialized tests discussed later in this guideline. These include measurement of airway reactivity (e.g., methacholine, mannitol, or histamine challenge) and specific inhalation challenge (SIC). Variability of airflow obstruction fundamentally distinguishes asthma from other obstructive disorders. Comparison of spirometry results before and after administration of a bronchodilator and variability of results when repeated over many days are effective and simple methods of assessing such variability.

When considering WRA, spirometry with bronchodilator is used primarily to document and quantify airflow obstruction. For this purpose, the forced expiratory volume in one second (FEV₁) and the ratio of the FEV₁ to the forced vital capacity (FEV₁/FVC ratio) are most useful. The average flow rate during the midportion of the expiratory maneuver (FEF_{25-75%}) may occasionally be useful.

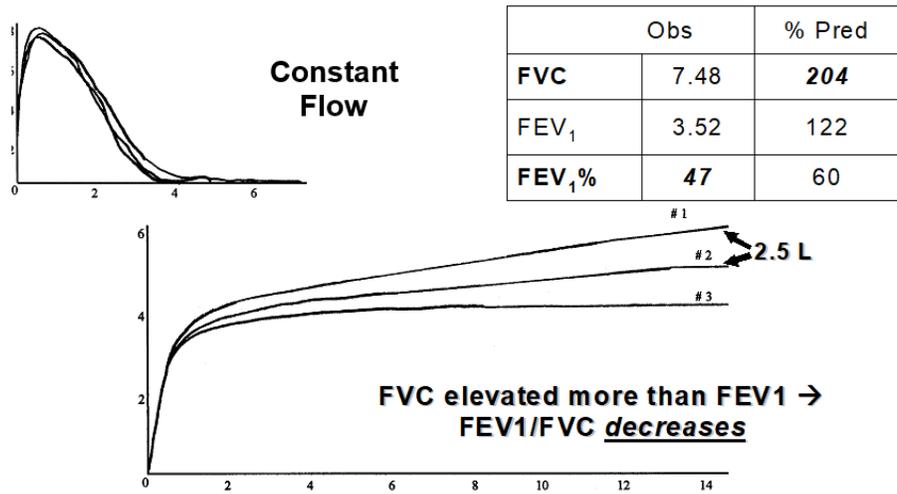
Asthma is confirmed by demonstrating airflow obstruction (e.g., by reduction in both FEV₁/FVC ratio and FEV₁) or by a positive methacholine challenge. Methacholine challenge testing is a specific test for airways reactivity in which FEV₁ is used as the test outcome, but it cannot clarify the work relationship or the particular antigen involved in work-related asthma. Repeated spirometry, or spirometry followed by repeated peak flow measurements, is used to demonstrate that the obstruction is present and that it is variable rather than fixed.

Methods

Accurate results depend upon use of proper equipment, proper test performance, and qualified interpretation. Considerations for spirometry quality assurance are not specific for WRA, and several excellent reviews are

available.^[100-102] OSHA has also recently issued guidance on best practices for occupational spirometry testing.^[103] ACOEM has emphasized the critical role of obtaining accurate data. The figures below illustrate common pitfalls.

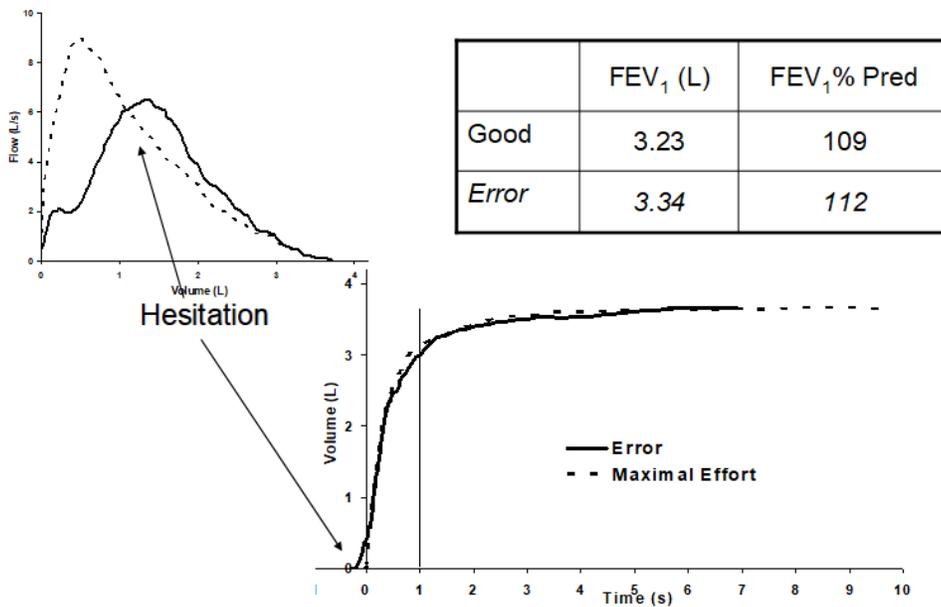
FIGURE 1. ERROR: INCONSISTENT ZERO-FLOW ERRORS CAUSING FLOWS TO BE OVER-RECORDED



DELETE THIS TEST. This spirometer’s zero-flow reference point was set at different incorrect levels before the first two maneuvers, causing the volume-time curves (bottom figure) to be splayed apart. FVC is more increased than FEV₁, falsely *reducing* the FEV₁/FVC and probably leading to an erroneous “obstructive impairment” pattern. Block sensor when the spirometer is zeroed and hold sensor still during subject testing to avoid this problem.

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med.* 2011;53(5):569-84.

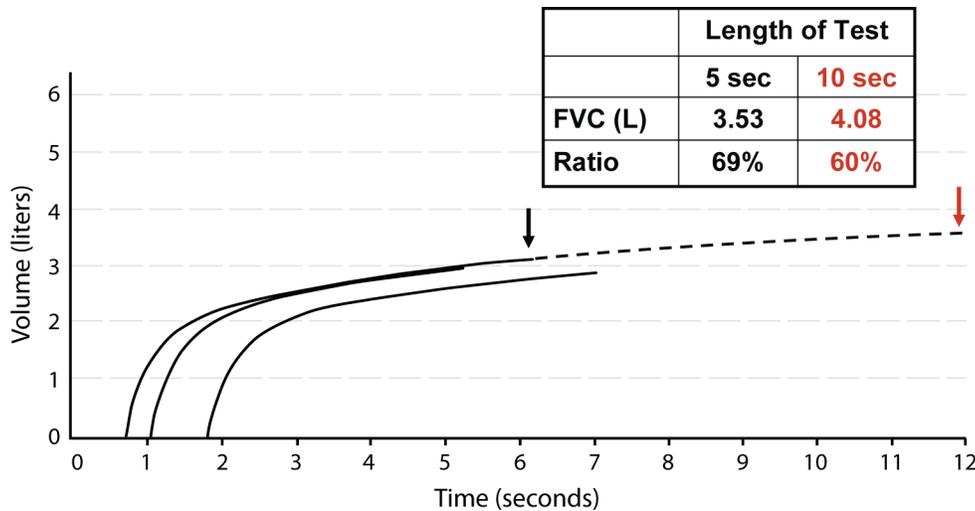
FIGURE 2. ERROR: EXCESSIVE HESITATION (SOLID CURVES)



DELETE THIS TEST. Since the worker's initial blast is delayed, the peak of the flow-volume curve (top figure) is displaced to the right, and a gradually climbing tail is seen at the start of the volume-time curve (bottom figure). Coach the worker: “BLAST out as soon as you are ready.”

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med.* 2011;53(5):569-84.

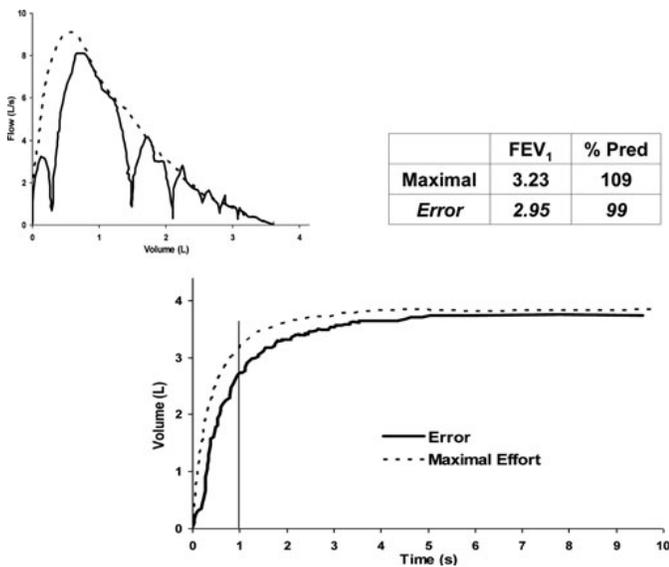
FIGURE 3. ERROR: EARLY TERMINATION (SOLID CURVES)



When an expiration stops before the volume-time curve flattens into a 1-second plateau, the FVC may not be fully recorded. An incompletely recorded FVC will falsely *increase* the FEV₁/FVC and may cause the spirometer interpretation to be “normal” even when airways obstruction is present. The solid lines show the curves that were terminated early. The dashed line shows the increase in “FVC” that would have occurred with only 5 more seconds of expiration. The more accurate FEV₁/FVC recorded after 10 seconds would trigger a correct interpretation of “airways obstruction.” (Note that no more than one maneuver should be recorded for longer than 15 seconds.) Coach: “Keep blowing until I tell you to stop.”

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med.* 2011;53(5):569-84.

FIGURE 4. COUGH IN FIRST SECOND—INVALID TEST (MUST BE DELETED)



Cough in the first second produces steep interruptions in the flow-volume curve and subtle steps in the first second of the volume-time curve. Coughs often reduce the FEV₁. Try offering a drink of water to solve this problem.

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med.* 2011;53(5):569-84.

Spirometry can be done alone or with pre- and post-bronchodilator testing. Pre- and post-bronchodilator testing is performed by establishing baseline airflow and then determining whether volumes increase with administration of a bronchodilating agent (usually albuterol, known internationally as salbutamol, a short-acting beta₂-receptor adrenergic agonist).

The American Thoracic Society (ATS) defines a 12% improvement in the FEV₁ or an absolute value increase of at least 200 mL after bronchodilator administration as indicating reversibility of airflow obstruction in FVC or FEV₁ values.^[6, 28, 95, 99, 100, 104-106] Rarely, subjects may have a paradoxical response to the bronchodilator resulting in increased obstruction; this is a transient effect associated with highly reactive airways responding to a nonspecific stimulus and slow response to the agent. Changes in peak flow are to be expected and are used to monitor progress in treatment but not for diagnosis.

Spirometry is difficult for some patients to perform, and irreproducible results may make interpretation difficult.^[107] Using spirometers that show large real-time graphical displays, testing should be performed by a technician who has completed NIOSH-approved spirometry course.^[103] Up to eight maneuvers may be attempted (beyond which most subjects tire) to produce three acceptable tracings, and the difference between the highest and second highest FVCs and FEV₁s should be within 0.15 of each other to achieve consistent “repeatable” results. The highest values of FVC and FEV₁ are used to summarize the patient’s lung function, regardless of whether they are drawn from the same or different curves. Inability to perform reproducible tracings is often due to failure to cooperate or poor effort because, properly performed, spirometry achieves a physiological limit on flow that is beyond voluntary manipulation. A small number of subjects will not be capable of producing reproducible tracings due to behavioral problems, poor neuromuscular coordination, or very low lung function. Such subjects often have a poor prognosis for survival and for future disease, even if their pulmonary function are within or close to the normal range.^[107-109] The American Thoracic Society and European Respiratory Society (ATS/ERS) have published 4 statements since 1979 on how to conduct spirometry tests and 2 statements since 1991 on how to interpret results.^[100, 110] Since 2000, ACOEM has published three comprehensive spirometry statements on conducting and interpreting tests, most recently in 2011.^[101] These statements emphasize the importance of performing and interpreting the results correctly.

Interpretation of Spirometry

Spirometry with or without bronchodilator cannot differentiate work-related asthma (WRA) from non-work-related asthma, and must be interpreted with additional information from the history or supplemental testing.^[111] Failure to demonstrate reversible airway obstruction on a single test day does not exclude the diagnosis of asthma or of airways reactivity in general.^[97, 99]

The following are important caveats to consider:

- Failure to demonstrate reversible airway obstruction on a single test day does not exclude asthma.
- Serial measurements can be used with clinical correlation to track progression and variability under different conditions and exposures, with the understanding that improvement in the measurements does not always correlate well with an improvement in the disease.
- Because asthma is characterized by variability, airflow obstruction is an indicator of status at any one time and does not necessarily reflect trends over time, but can indicate worsening of disease if it is much worse than a previous FEV₁ measurement.
- Therefore, its main value is in demonstrating variability (e.g., ruling out irreversible obstruction).^[28, 90, 99, 100, 104, 112]

The measurements of greatest utility in spirometry for the evaluation of airways disease are as follows ^[102, 104]:

- Forced expiratory volume in one second (FEV₁), expressed in liters and/or as a percentage of predicted values
- FEV₁ before and after (pre/post) administration of a bronchodilator, usually albuterol (salbutamol)
- Pre/post FEV₁, which is measurement of FEV₁ before and after (pre/post) a work shift, taking into account diurnal variation
- Ratio of FEV₁ to forced vital capacity (FEV₁/FVC), expressed as a percentage
- Peak expiratory flow (PEF), expressed primarily in liters per minute, which is particularly useful in following workers in whom reactive airways are demonstrated
- Of less central importance, forced expiratory flow rate (FEF₂₅₋₇₅), which is the volume expired between 25% of FVC and 75% of FVC, often called midflows (see limitations below)

Variability in appropriate spirometry measures in testing separated in time (days) or in response to bronchodilators (most accurately for FEV₁) indicates asthma. Fixed airways obstruction is present when volumes are unchanged, within limits of the test.

Although FEF₂₅₋₇₅ is a measure of airflow through smaller airways (structures that are commonly and disproportionately affected by cigarette smoking), FEF₂₅₋₇₅ tends to vary far more than the FEV₁ both within and between healthy individuals; thus, it is difficult to interpret abnormality of this flow rate in individual patients. When early emphysema is present, airflow in small airways is disproportionately reduced and is less variable than in asthma, but standards for this interpretation have not been established. Since 1991, ATS has discouraged using FEF₂₅₋₂₅ to diagnose small airways disease in individual patients when FEV₁ and FEV₁/FVC are in the normal range.

Spirometry with bronchodilator is not invasive, has few adverse effects, is low to moderate cost, and is high in yield for complications and other respiratory problems. Its value comes in correlation with clinical information and observation. Spirometry with bronchodilator is thus recommended as an integral part of the evaluation of work-related asthma.

Peak Expiratory Flow Rates (PEFR)

Peak expiratory flow rates (PEFR) is defined as the maximum flow achieved during expiration, delivered with maximal force, starting from the level of maximum inspiration and using simple portable meters. Serial PEFR measure the circadian rhythm, which has lower values in the early hours of the morning and maximal in the afternoon. The differences are more pronounced in individuals with bronchial asthma.^[113]

The use of PEFR is common in the diagnostic investigation of asthma including work-related asthma, both work-exacerbated and OA. PEFR is most readily performed via a hand-held peak flow meter providing air flow measurement in liters/minute, and must be performed by the patient outside of a medical setting to be useful in evaluation of WRA.^[114-116] Thus, PEFR can be easily obtained both at and away from work to document presence or absence of changes in flow that are potentially related to the workplace environment or exposures.

Peak Expiratory Flow Rates (Serial Measures) for Diagnosing Work-Related Asthma

Serial peak expiratory flow measurements are moderately recommended as an initial evaluation method for diagnosing work-related asthma, in patients already diagnosed with asthma by other methods. The physician or qualified staff should train the patient on the proper use of the meter and the importance of accurate recordings. A meter that can store the measurements should be used when possible.^[7, 86, 117-119]

Strength of Evidence – Moderately Recommended, Evidence (B)

Level of Confidence – High

Performed – Assessment of serial measurements of PEFR at and away from work is an accessible method of confirming the relationship between the exposure and bronchoconstriction and has been recommended as a first-line investigation in suspected cases of WRA.^[120] Standards for PEFR devices and their performance have been published by ATS and the subcommittee on Occupational Allergy of the European Academy of Allergy and Clinical Immunology group with recommendations for total duration and frequency of PEFR measurements both at and away from work.^[120] The optimal frequency and duration of serial PEFR has not been agreed upon. Generally, workers are instructed to record PEFR every 2-3 hours for 4 weeks, including periods at and away from work, while maintaining a diary indicating their activities, as well as any symptoms they might be experiencing, including use of bronchodilators. Dedicated diary cards are available at www.occupationalasthma.com. Each measurement session should include three or more forced expiratory maneuvers with the best of the attempts recorded and used for analysis.^[1, 3, 7, 9, 113, 116] The best of three PEFR readings should be recorded on each occasion, provided the best two readings were within 20 L/minute of each other. A recording period of 4 weeks, including a period of at least 2 weeks away from suspect exposure, is recommended, although longer periods increase the value of the test.^[114-116] PEFR measures should be obtained upon awakening, mid-day, at the end of the shift, and before bedtime (or comparable times for non-day shift workers), although some investigators recommend every 2 hours while awake.

There are several interpretive methods for analysis of serial PEFR data. Values must be plotted with the average reading for time of day for work and off-work periods. Analysis may be performed visually by an expert, although there is a degree of intraexpert and interexpert variability.^[121] Two alternative methods include difference in diurnal

variability (maximum-minimum/maximum value x 100) and differences in mean PEF between work and non-work days. The difference between mean PEFR on rest days and mean PEFR on work days has been recommended as the best index for differentiating workers with WRA from those with non-WRA by Anees et al. They proposed a value of >16 l/minute as the most sensitive index to differentiate subjects with WRA from healthy individuals and those with non-WRA.^[115]

Indications – To assist in screening patients with a history consistent with WRA.^[9, 115, 119] There have been concerns over the reliability of self-reported peak flow measurements. One study found that self-recorded PEFRs were concordant with less than half of electronically stored measurements.^[122] Although other investigators have reported better concordance,^[123] these findings emphasize the importance of careful monitoring and daily supervision of workers during performance of serial PEFR measurements. Use of a freely downloadable automated data plotting and analysis system may limit human variability in interpreting the PEF values, and can be particularly useful for practitioners without extensive prior experience (www.occupationalasthma.com).^[124-129]

Harms – None.

Benefits – Can provide moderately objective evidence of relationship between work and asthma worsening.

Advantages and Limitations – PEFR is heavily dependent upon the worker's efforts, including reliable performance of a forced expiratory maneuver, and accurate recording of the results; it also assumes worker honesty in performing and recording the test results.^[1, 3, 95, 112] In a study of 17 subjects blinded to simultaneous recording by the peak flow meter, only 55% of the records were completed accurately by the participants.^[6] Quirce et al reported that 23% of PEF readings were inaccurate and 23% of the readings were invented, although these did not tend to change interpretation of work-relatedness.^[122] PEF measures cannot differentiate between OA and work-exacerbated asthma.^[7]

Rationale for Recommendation

There are 4 moderate-quality studies that support the use of PEFR as an investigational tool for the diagnosis of WRA.^[114, 116, 119, 127] Three studies performed compared PEFR readings to FEV₁/FVC measurements over a 4-week period in workers with a diagnosis of OA, concluding that serial PEFR measurements over a 4-week period including a period away from the workplace was moderately sensitive and specific. There is a suggested “minimum data criterion” of ≥4 readings per day for more than 2 weeks that should be met before analysis of the data.^[114, 116, 119] Another study demonstrated similar results over a shorter period of time with the use of a specific analysis tool.^[126, 127] There is evidence that both supervised and unsupervised PEFR methods are acceptable; thus, no recommendation for or against a particular method is made, and is left to the discretion of the treating physician for each particular patient.^[112, 130] There is one high-quality study demonstrating poor sensitivity with a cross-shift technique.^[118] PEFR is non-invasive and low cost. Serial PEFR is recommended as an initial method for investigating suspected WRA. It is desirable to initiate serial PEFR early in the evaluation of WRA when patients are more likely to still be exposed to a putative cause of asthma. Serial peak expiratory flow measures are relatively inexpensive, have a low risk of adverse events, and may add information on airway resistance both at work and at home and are thus recommended. This recommendation was downgraded from strongly recommended to moderately recommended due to the technical challenges and the ability to manipulate the results.

EVIDENCE FOR THE USE OF PEAK EXPIRATORY FLOW RATES

There are 2 high-^[112, 130] and 6 moderate-quality^[114, 116, 118, 119, 126, 127] studies incorporated into this analysis.

Nonspecific Bronchial Provocation Test

Establishing a diagnosis of WRA must start with confirmation of the presence of asthma. Bronchoprovocation with methacholine, histamine, cold air, mannitol, or exercise challenge is used to establish the diagnosis of asthma, particularly when asthma is suspected and spirometry is normal or near normal. Methacholine and histamine challenges are the most commonly available tests.^[17, 131] Methacholine is preferred to histamine because it is associated with fewer side effects, and lung function measurements are more reproducible.^[132] Nonspecific bronchial provocation testing is thought to reflect the increased sensitivity of the airways to inhaled nonspecific stimuli or irritants that is reported by many patients with asthma.^[131, 133] These stimuli are thought to evoke airflow limitation predominately by an effect on airway smooth muscle, although the mechanisms preceding this effect differ. Persistence of bronchial hyperresponsiveness out of the workplace is more likely in those with longer duration of symptoms and exposure than in workers with early diagnosis and removal. Increased methacholine

reactivity may resolve a few months out of exposure, but has been demonstrated to persist for more than 13 years out of exposure.

Nonspecific Bronchial Provocation Test for Diagnosing Work-Related Asthma With Compelling Clinical History

Nonspecific bronchial provocation test (e.g., methacholine) is strongly recommended for use in diagnosing asthma if the clinical history is compelling and other tests (spirometry and bronchodilator responsiveness) are unhelpful.

Strength of Evidence – Strongly Recommended, Evidence (A)
Level of Confidence – High

Nonspecific Bronchial Provocation Test for Diagnosing Work-Related Asthma

Nonspecific bronchial provocation test (e.g., methacholine) is moderately recommended for use in diagnosing work-related asthma as other steps are required to establish the work-relatedness of the asthma.

Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – High

Mannitol Bronchial Provocation Test for Diagnosing Work-Related Asthma

Mannitol bronchial provocation test is recommended for use in diagnosing work-related asthma; other steps are required to establish the work-relatedness of the asthma.

Strength of Evidence – Recommended, Evidence (C)
Level of Confidence – Moderate

Performed – Testing location should be experienced and technicians properly trained on performance of spirometry.^[132] There are two methods for inhaling aqueous solutions of pharmacologic stimuli: 1) the 2-minute tidal breathing protocol; and 2) 5-breath dosimeter protocol.^[131, 132, 134, 135] The method of performing nonspecific bronchial provocation tests is to first measure baseline lung function and to calculate a target FEV₁ that indicates a 20% fall in FEV₁. Inhalation of a placebo or diluent (0.9% NaCl) is optional. Inhalation of the bronchoconstrictor agent methacholine typically starts at a concentration of 0.031 to 0.0625 mg/mL, and then increases by doubling or quadrupling concentrations up to 16, 25, or 32 mg/mL, depending on the protocol. Following each inhalation, the FEV₁ is measured and the test is stopped when the FEV₁ has fallen by 20% from baseline or diluent value. The response is usually expressed as a provocative concentration (PC₂₀) producing a 20% fall in forced expiratory volume in 1 second. The presence of asthma is usually defined as a ≥20% fall in the FEV₁ at a methacholine dose of 4 mg/mL or below.^[74, 136-140] Methacholine 4-16 mg/mL is considered borderline full categorization of bronchial responsiveness based on methacholine PC₂₀ mg/mL dose.⁴ Mannitol testing is performed via inhalation of increasing doses of dry mannitol powder in capsules, up to 160 mg. The test is considered positive if the cumulative dose of mannitol inducing a 15% decrease in FEV₁ is 635 mg or less. The dosing is sequential, starting at 5 mg, and increasing to doses of 10, 20, 40, 80, and 160 mg. The 160-mg dose may be repeated two additional times for a cumulative possible dose of 635 mg.^[141-144]

Criteria and Standards for Use – Bronchial challenge testing should be done according to the 1999 ATS statement and the 1993 European Respiratory Society statement.^[90, 144]

⁴According to ATS *Guidelines for Methacholine and Exercise Challenge Testing –1999*, the categories of bronchial responsiveness by methacholine dose (PC₂₀ mg/mL) are as follows:

- >16 is normal bronchial responsiveness;
- 4.0-16 is borderline BHR;
- 1.0-4.0 is mild BHR (positive test); and
- <1.0 is moderate to severe BHR.

Before using this categorization, the following must be true: baseline airway obstruction is absent; spirometry quality is good; and there is substantial postchallenge FEV₁ in response to bronchodilator.

Indications/Contraindications – To establish the diagnosis of asthma and to aid in the diagnosis of WRA. NSBP is not generally recommended if the baseline FEV₁ is <65% of predicted.^[1, 5] Absolute contraindications for methacholine challenge testing include:

- severe airflow limitation (FEV₁<50% predicted or <1.0L), heart attack, or stroke in previous 3 months;
- uncontrolled hypertension (systolic BP>200 or diastolic BP>100); and
- known aortic aneurysm.^[132]

Relative contraindications include:

- moderate airflow limitation (FEV₁ <60% predicted or <1.5L;
- unable to perform acceptable-quality spirometry;
- pregnancy;
- nursing mothers; and
- current use of cholinesterase inhibitor medication (for myasthenia gravis).^[132]

Harms – Bronchoconstriction, transient symptoms of wheezing, cough, mild dyspnea, and chest tightness, with smaller risk for dizziness and headaches post-test.

Benefits – Accurate diagnosis of asthma.

Advantages and Limitations – Testing for airway hyperresponsiveness is relatively objective; due to its accessibility, it is used regularly in clinical practice. It is limited in differentiating work-related asthma from non-work-related asthma without additional history, testing, and information. Methacholine challenge testing is more useful in excluding a diagnosis of asthma than in establishing a diagnosis because its negative predictive power is greater than its positive predictive power.^[132] Bronchial hyperresponsiveness with methacholine challenge testing may also be seen in conditions other than asthma, including smoking-induced chronic airway obstruction, congestive heart failure, cystic fibrosis, bronchitis, and allergic rhinitis.^[132]

Rationale for Recommendations

Many high- and moderate-quality studies have evaluated the diagnostic utility of nonspecific bronchial challenge testing in comparison to other studies including specific inhalational challenge testing, peak expiratory flow meters, and immunological testing to establish the diagnosis of work-related asthma.^[58, 74, 90, 139, 140, 145-167] In one study of dairy farmers, the sensitivity and specificity of methacholine challenge compared to bovine inhalational challenge in diagnosing OA were reported to be 82% and 65%, respectively.^[146] Another study comparing specific inhalational challenge to nonspecific bronchial challenge testing reported a sensitivity of 57% and a specificity of 93% for OA.^[153]

Methacholine and histamine challenges are reported to be more reliable than other nonspecific bronchial provocation tests.^[140, 165] Overall, methacholine challenge testing has been reported to have a sensitivity level of around 95% in the diagnosis of asthma.^[97] A major caveat is that nonspecific bronchial provocation testing is not capable of reliably differentiating between WRA and non-work-related asthma.^[69, 138] The temporal relationship of nonspecific bronchial hyperreactivity (NSBHR) with exposure is important^[168] and the test should be performed either during or immediately after the work shift if possible. The authors considered a two-fold increase in the PC20 FEV₁ after removal of exposure to be significant.

Methacholine challenge tests do not always remain positive after a diagnosis of WRA, as methacholine reactivity may wane out of exposure. In a case report, a worker with asthma secondary to toluene diisocyanate (TDI) lost his reactivity to methacholine after 2 months of removal from exposure.^[169] Other studies of workers with OA to TDI,^[170] cobalt,^[171] and reactive dyes^[172] have demonstrated persistent bronchial hyper-responsiveness in some from 5 to 13 years out of exposure. Those with asthma from HMW agents may also demonstrate persistent airways hyperresponsiveness.^[173] Workers were more likely to lose their methacholine responsiveness with early diagnosis and early removal from exposure after onset of asthma. Those who became asymptomatic out of exposure were more likely to revert to normal bronchial reactivity than those who reported ongoing asthma symptoms.^[133]

Compared to specific inhalational challenges, bronchoprovocation is less hazardous, lower cost, easier to perform, more readily available, and can be completed in less time. Therefore, it is recommended for the diagnosis of asthma, and work-related asthma, particularly when the baseline spirometry is normal yet there is sufficient index of clinical suspicion.

Although most bronchoprovocation agents cause a fall in the FEV₁ by triggering bronchial smooth muscle contraction, different agents act through different pathways to achieve this effect. Methacholine acts as a non-selective muscarinic agonist on receptors on bronchial smooth muscle, whereas histamine acts through stimulation of H1 receptors on bronchial smooth muscle, or indirectly through stimulation of vagal parasympathetic reflex bronchoconstriction. Cold air leads to respiratory heat and water loss with transient hyperosmolarity in the respiratory mucosa, triggering mediator release from eosinophils or mast cells that cause the airways to narrow. Mannitol likely triggers the release of inflammatory and/or bronchospastic mediators, causing the smooth muscle of the airway to contract and resulting in airway narrowing. The exercise challenge is thought to cause inflammatory cells to release mediators such as leukotrienes, prostaglandins, and histamine that secondarily provoke airway smooth muscle constriction and a measurable fall in the FEV₁.

Evidence for the Use of Nonspecific Bronchial Provocation Test

There are 9 high-^[70, 90, 145, 146, 151, 157, 161, 165, 174] and 22 moderate-quality^[55, 58, 74, 136, 137, 141, 142, 144, 149, 156, 158-160, 162, 163, 167, 175-180] studies incorporated into this analysis. There are 9 other studies in Appendix 1.^[139, 148, 150, 181-186]

Specific Immunological Testing

Specific immunological testing to suspected allergens is commonly used to aid in the diagnosis of allergic rhinitis and OA.^[146, 167, 187-194] These tests are performed to evaluate type I (IgE) hypersensitivity reactions to specific allergens^[148, 167] and can be useful in the diagnosis of certain cases of OA caused by immune or allergic mechanisms, in contrast to irritant-induced asthma. However, the presence of specific antibodies is an indicator of an immune response and does not necessarily have a causal relationship with occupational asthmatic symptoms. Hence, demonstration of sensitization to an occupational agent by specific IgE and/or skin testing alone, without demonstrating the work-relatedness of the asthma, is insufficient to establish a diagnosis of OA.

Detection of IgE to a specific allergen is accomplished by skin prick testing (SPT) and serum IgE testing when kits are available for the specific allergen. For more information on skin testing, see the following section. Three methods of detecting serum IgE antibodies have been used to assess antigenicity to occupational antigens: 1) RAST; 2) ELISA; and 3) ImmunoCAP. In addition to basing recommendations on the available literature that compare and validate a particular method, this guideline also considers the commercial availability of these assays.

The sensitizing agents known to induce OA are traditionally divided into high-molecular-weight (HMW) and low-molecular-weight (LWM) antigens. The allergens and extracts are better characterized and available for HMW antigens, and much less so for LMW antigens.

High-Molecular-Weight Agents

Occupational asthma (OA) induced by HMW agents, which are mainly proteins of animal or plant origin, is often associated with the production of allergen-specific IgE antibodies. Once sensitization has occurred, subsequently inhaled allergens bind and cross-link allergen-specific IgE present on the surface of mast cells and basophils. This cell surface perturbation triggers these cells to release an array of allergic and inflammatory mediators that give rise to the asthmatic response.^[191] Examples of HMW asthmagens include:

- proteins of biological origin, such as laboratory animals;
- enzymes used in the detergent or food industries;
- grain proteins found in bakeries; and
- natural rubber latex proteins prevalent in health care workers.

Such proteins are considered complete allergens, capable of causing the elaboration of specific IgE antibodies. Also, for the most part, commercial validated assays exist for most common HMW allergens; therefore, recommendations will be made for the class as a whole.

Low-Molecular-Weight Agents

LMW agents that induce OA are incomplete antigens or haptens that become allergenic only after binding with one or more autologous serum, epithelial, or tissue proteins.

Common LMW agents include:

- diisocyanates;
- colophony fume, liberated from cored solder in the electronics industry;
- complex platinum salts; and
- the family of acid anhydrides, which are common constituents in the manufacturing of resins.

Specific IgE to the hapten-protein conjugate (frequently human serum albumin) is detectable in some but not all cases of asthma, and sensitivity varies with each agent. Several reasons have been proposed. Unlike the HMW agents that are complete antigens, LMW chemicals may couple variably to a protein to form a complete hapten-protein complex. The process may form new and unique antigenic determinants that are not shared by different affected workers. Waning of the immune response since last exposure, and the lack of standardization of laboratory assays are additional factors that make testing difficult.^[195-197] Thus, interpretation of testing results must include consideration of the sensitivity and specificity of the test for the suspected agent. For example, specific IgE antibodies have been detected to anhydride acids, trimellitic, and tetrahydrophthalic anhydrides^[198, 199] but not to maleic anhydride.^[200] Although the allergic reaction to platinum salts is considered to be type 1 IgE mediated, there is no commercially available radioimmunoassay and the detection of specific IgE antibodies to complex (unconjugated) halide platinum salts by skin-prick test is considered more sensitive. Specific IgE antibodies to colophony and diisocyanates, two important causes of LMW OA, are poorly characterized. No reliable method of antibody detection for colophony-fume asthma has been established.^[201] For asthma induced by diisocyanates, the presence of specific IgE antibodies to a diisocyanate-human serum albumin (HSA) conjugate is relatively insensitive, being found in less than half of clinically confirmed cases of diisocyanate-related OA.^[202, 203] Investigators who have evaluated the sensitivity and specificity of diisocyanate-specific IgE to diagnose OA have demonstrated an association with diisocyanate asthma, but inadequate sensitivity to be used as screening tools.^[203, 204] This difficulty may in part be caused by the variability of serologic methods used in the various studies,^[205] and in part because different antigens are formed from these highly reactive chemicals that can differ between individuals and types of exposure. Thus, no one particular antigen has been identified for all cases of diisocyanate-induced asthma.

The lack of assay standardization is an important drawback to the detection of LMW IgE antibodies, as most studies have reported results using in-house assays that are not commercially available.^[205] In addition, there is no consensus in conjugate preparation, although vapor hapten-albumin conjugates have been reported as having greater sensitivity.^[205] Finally, the method of making the asthma diagnosis has varied between studies, causing difficulty in interpreting the sensitivity and specificity of serologic results.^[206]

The role of specific IgG is also unclear.^[201, 205] Studies that have investigated HMW IgG antibodies among laboratory workers and bakers have found a correlation with exposure intensity, but not a significant relationship with allergic symptoms.^[207, 208] IgG4, a subtype of IgG, may be associated with the development of tolerance rather than allergy. Several studies have found that specific IgG responses to diisocyanate/HSA conjugates are also generally associated with exposure^[205, 209, 210] and not disease.

IgE-Specific Immunological Testing for High-Molecular-Weight Specific Antigens

Specific immunological testing (IgE) is strongly recommended for workers with symptoms consistent with occupational asthma (OA) to certain high-molecular-weight specific allergens and when standardized antigens and assay protocols exist. The specificity and sensitivity of the allergens should have been evaluated in quality studies using validated test methods that are commercially available. High-molecular-weight allergens for which there is sufficient evidence in quality studies include flour dusts, bovine danders, laboratory, and other animal allergens. Natural rubber latex (NRL) allergy can be confirmed by serum IgE testing, but the assay does not include all potential NRL allergens, such that a negative result does not necessarily exclude the diagnosis of NRL allergy.

Strength of Evidence – Strongly Recommended, Evidence (A)
Level of Confidence – High

IgG-Specific Immunological Testing for High-Molecular-Weight Specific Antigens

Specific immunological testing (IgG) is not recommended as a diagnostic tool for select workers with symptoms consistent with occupational asthma (OA) to high-molecular-weight specific allergens. It can be used for a marker of exposure to certain allergens, but in and of itself does not diagnose disease.

Strength of Evidence – Not Recommended, Evidence (C)
Level of Confidence – High

IgE-Specific Immunological Testing for Low-Molecular-Weight Specific Antigens

Specific immunological testing (IgE) is not recommended for workers with symptoms consistent with occupational asthma (OA) to low-molecular-weight specific allergens due to low sensitivity and specificity and lack of method validation.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)
Level of Confidence – Moderate

According to the Practice Parameters of the American Academy of Allergy, Asthma & Immunology, specific allergens need documented evaluation in quality studies with reported specificity and sensitivity and using standardized antigens and assay protocols. In addition, they need to be commercially available before they can be considered reliable for routine evaluation of workers. This is not the case for LMW test antigens, which are usually prepared and evaluated in individual research laboratories and are not in general commercially available. A more detailed rationale for the recommendations follows below.

Performance – The assay should improve on disease prediction by demonstrating high sensitivity and specificity. Methods for testing antibodies need to be standardized, with established population norms to guide interpretation of results. Each assay needs to be performed according to the manufacturer's recommendations following a proper protocol for testing.^[211] The majority of LMW antigens do not have commercial assays that have been validated for specific antibody testing.

Indications – To be used for allergens that have been shown to have acceptable sensitivity, specificity, positive predictive value, and negative predictive value using a validated method in investigational studies.^[211, 212] If no studies have been conducted for the agent(s), no recommendation is made.

Harms – None.

Benefits – Non-invasive relatively inexpensive method of establishing sensitization to suspect agent.

Advantages and Limitations – Not all OA is believed to have IgE and/or IgG mediated immune responses, but data suggest IgE is involved in subsets of symptomatically exposed workers, especially to HMW antigens.^[202, 213] There are unique challenges with such testing for work-related asthma. The reported half-life for specific IgE in serum, the time available for specific immunological testing, is approximately 7 hours. In tissue, it has varied from a short half-life of approximately two days^[189] to 5.8-6.7 months.^[202] Specificity and sensitivity differ by allergen and time since exposure.^[146-148, 167, 188, 190, 199, 202, 213, 214] Without accurate exposure data including time since exposure, a negative specific IgE may lead to a misdiagnosis and false conclusions about the disease. There is documented cross-reactivity between different isocyanates, which may confound the determination of causation in some cases.^[202, 208] Different laboratories and commercial tests have not been validated with proper homogeneous controls.^[3, 213] This variability creates difficulty in creating overall recommendations for immunological testing.

Rationale for Recommendations

High-Molecular-Weight Agents:

Wiszniewska et al. reported a sensitivity of 61.6%, specificity of 77.3%, PPV 71.5%, NPV 68.5% in workers with baker's asthma to wheat flour.^[215] Van Kampen 2008 reported sensitivity of 61-87%, specificity of 68-94%, PPV 74-95%, NPV 56-82% in workers with baker's asthma to wheat/rye flour.^[216] Another study evaluating IgE to bovine dander reported sensitivity of 82%, specificity of 100%, PPV 100%, and NPV 89%.^[146] A moderate-quality study reported smoking and generalized atopy also were independently significantly associated with positive IgE to grain dust ($p < 0.05$).^[167] Platts-Mills et al. reported IgE was more specific in workers exposed to rats with symptoms of asthma and rhinitis than IgG was.^[203] IgG levels were reported to show evidence of exposure to wheat flour, but did not have a correlation with allergic symptoms in bakers.^[207] IgE levels were also elevated in workers with self-reported respiratory symptoms compared to controls in a feed plant.^[217] Other studies also reported positive IgE to HMW allergens in patients diagnosed with OA by SIC.^[218]

Low-Molecular-Weight Agents:

Park et al. evaluated IgE levels in patients with work-related asthma to reactive dyes.^[219] The authors reported a sensitivity of 53.7%, specificity 86.0%, PPV 62.9%, and NPV of 80.8%. For diisocyanates, Lushniak et al. reported a small study where IgG was a marker of exposure, but not of OA in a group of workers exposed to MDI.^[208] Bernstein et al. reported a sensitivity of IgE to isocyanates of 21% and a specificity of 89%.^[147] Tee et al. reported IgE related to diisocyanate exposure as highly specific at 91-100% in patients investigated for OA and confirmed with specific inhalational challenge testing, but with a sensitivity of 19-28%. Therefore, it is a useful test if it is positive, but a negative test is less informative.^[202] Budnik et al. reported no false-positive results with IgE or SPT testing in patients exposed to MDI with asthma confirmed by positive specific inhalational challenge testing.^[205]

Evidence for the Use of Specific Immunological Testing

There are 6 high-quality^[146, 190, 202, 205, 215, 216] and 12 moderate-quality^[147, 167, 187, 188, 191, 203, 204, 207, 213, 214, 217, 218] studies incorporated into this analysis. There are 5 other studies in Appendix 1.^[148, 193, 199, 211, 212]

Skin Prick Testing

Skin tests are used, in addition to a directed history and physical exam, to exclude or confirm sensitization in IgE-mediated diseases, including asthma. There are two types of skin testing used in clinical practice. These include percutaneous testing (prick or puncture) and intracutaneous testing (intradermal). Prick testing involves introducing a needle into the upper layers of the skin through a drop of allergen extract and gently lifting up the epidermis. Intracutaneous (intradermal) testing involves injecting a small amount of allergen (0.01-0.02 mL) into the dermis. If local tissue mast cells have surface IgE specific for the allergen being tested, it will cross-link the IgE and trigger the release of preformed histamine from mast cells which in turn causes increased vascular permeability and development of a wheal; inflammatory mediators initiate a neural reflex causing vasodilatation, leading to erythema (the flare). Test results often report the size of the wheal and the size of the flare in millimeters, as W/F mm/mm and compared to the negative saline control response. Results may also be reported on a scale of 0 to 4+, where 1+ is erythema smaller than a nickel in size, 3+ is wheal and erythema, and 4+ is a wheal with pseudopods and erythema. Testing is most often performed with various allergens placed on the skin of the volar forearm or the back.^[150, 220, 221] Although the back is more reactive, the difference is minimal. Prick testing methods are the preferred initial technique for detecting the presence of IgE. They correlate better with clinical sensitivity and are more specific but less sensitive than intradermal testing.^[222] Most of the literature suggests that with a negative skin prick test result, a positive intradermal skin test (IDST) result adds little to the diagnostic evaluation of inhalant allergy. IDST is only indicated and should be selectively used when there is a compatible or compelling history and a negative or equivocal SPT result.^[223] Many studies have demonstrated that the prick skin test response correlates much better with clinical allergy.^[224]

Skin prick testing has been used to assess allergy to asthmagens in various types of patients and occupational settings.^[62, 74, 190, 219-221, 223, 225-229] This systematic review will synthesize the skin prick testing literature as it directly relates to other diagnostic methods for OA, but will not incorporate the entirety of allergic skin testing for common allergens.^[227] Not all allergens have the same level of investigative studies to validate skin prick testing as an authoritative diagnostic test. Workers should be referred to a physician with experience in skin prick testing for interpretation to assess atopy, as well as to the potential causative allergen. Skin prick testing should be performed by trained and qualified personnel, and the tests supervised by and interpreted by a physician experienced in the technique.^[224]

Skin Prick Testing for High-Molecular-Weight Allergens

Skin prick testing is strongly recommended for high-molecular-weight allergens for select workers with symptoms consistent with occupational asthma (OA) to specific allergens and where validated, commercial skin testing extracts are available. High-molecular-weight allergens for which there is sufficient evidence are natural rubber latex, wheat and rye flour, grain dust, alpha-amylase, bovine danders, and laboratory and other animal allergens.

Strength of Evidence – Strongly Recommended, Evidence (A)
Level of Confidence – High

Skin Prick Testing for Low-Molecular-Weight Allergens

Skin prick testing is moderately recommended for low-molecular-weight allergens for select workers with symptoms consistent with occupational asthma (OA) to specific allergens, and where skin testing extracts are available. Low-molecular-weight allergens for which there is sufficient evidence are reactive dyes, halogenated platinum salts, and trimellitic anhydride.

Strength of Evidence – Moderately Recommended, Evidence (B)

Level of Confidence – Moderate

Skin Prick Testing to Other Allergens Not Covered Above

Skin prick testing is not recommended for allergens not covered above. When specific allergens have not been evaluated in quality studies with reported specificity and sensitivity, skin prick testing for these allergens cannot be recommended.^[215, 230] Skin prick testing is also not recommended if suspected cause is non-allergenic.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – High

Performed – The performance of skin prick testing has been the subject of a practice guideline by the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI)^[231] Skin prick tests should be performed with 1.0 mg/mL histamine dihydrochloride as the preferred positive control and normal saline or 0.5% glycerin-saline as the negative control.^[190, 224, 228, 232] Histamine control tests should be read 15 minutes after application to determine their peak reactivity. Concurrent use of antihistamines, H₂ antagonists, tricyclic antidepressants and other medications impair histamine responsiveness and may reduce the size of the skin test response or suppress it altogether. Several physiologic factors may affect interpretation of skin test results, including skin pigmentation and endogenous cortisol. Different devices used for skin testing result in variable degrees of trauma imparted to the skin and may thereby produce different sizes of positive reactions. Thus, consistent criteria are needed to rate a positive reaction produced by different skin test devices. Positive tests are often defined as a mean diameter of wheal larger by 2-3 mm more than the negative control and/or an erythematous reaction larger than 10-21 mm.^[146, 190, 228, 232] Skin tests should not be performed at skin sites with active dermatitis. Adequate equipment to treat anaphylaxis must be available, although this is very rare with prick skin testing.^[231]

FIGURE 5. PERCUTANEOUS ALLERGY SKIN TEST RESULTS



Measuring the wheal and flare. Reprinted courtesy of Dr. Hal Nelson.

Each individual extract is often prepared differently and this process should be well understood by the practitioner. Frequently, a dilute preparation of an extract that is appropriate for skin prick testing is not commercially available and must be prepared by the practitioner. The stability and potency of allergen extracts are important issues that affect skin test results. Allergen extracts deteriorate with time, accelerated by dilution and higher temperatures, and lead to smaller or absent skin test responses. Some extracts such as molds

contain proteases that degrade other extracts if mixed together. Expiration dates should be checked on a regular basis. Cross-contamination or bacterial contamination should be prevented, and all extracts should be stored under cold (4°C) to ensure stability.

Indications – Prick skin testing should be performed with allergens that have acceptable sensitivity, specificity, positive predictive value, and negative predictive value.^[232, 233] Allergens associated with OA and that meet these criteria include: natural rubber latex, wheat and rye flour, grain dust, alpha-amylase, reactive dyes, bovine danders, laboratory and other animal allergens, halogenated platinum salts, and trimellitic anhydride.

Harms – Rare risk of severe asthmatic or anaphylactic reactions.

Benefits – Minimally invasive, inexpensive, and has few adverse events.

Advantages and Limitations – Skin prick testing is minimally invasive, has few adverse events, is moderately inexpensive and is recommended for specific cases where the allergen extracts have known sensitivity, specificity and those results are reliable. The risk of fatality due to skin prick testing is extremely remote, and severe/anaphylactic reactions are rare. Nevertheless, this risk cannot be completely excluded in highly susceptible subjects, such as individuals with a history of previous anaphylactic reactions, pregnant women, those who have uncontrolled asthma, or have high degree of reactivity. Skin testing should not be performed in pregnant women and only in other high-risk individuals where the consequence of the result outweighs the risk.^[234]

Rationale for Recommendations

Multiple studies include skin prick testing as part of the diagnostic protocol, although most include skin prick testing as a test for atopy rather than a diagnostic test for OA.^[227] However, there are 20 high- or moderate-quality studies that provide results of skin prick testing compared to specific inhalational challenge testing for the diagnosis of OA.^[146, 148, 150, 190, 213, 220, 225] For patients with OA related to enzymes used in baking and pharmaceuticals confirmed by specific inhalational challenge testing, the sensitivity of skin prick testing was 100% and specificity was 93%.^[216, 220, 232, 233] Wiszniewska, et al., reported a sensitivity of 42%, specificity of 86%, PPV 73%, NPV 61% for skin testing in workers with baker's asthma to wheat flour.^[215] In workers exposed to reactive dyes, the sensitivity of skin prick testing was 76% and the specificity was 91% for OA.^[190] In a study of platinum salt workers, SPT was used to confirm sensitization in individuals with work-related asthma.^[230, 235, 236]

Evidence for the Use of Skin Prick Testing

There are 8 high-quality^[70, 146, 190, 215, 216, 232, 233, 237] and 12 moderate-quality^[62, 218, 220, 225, 230, 235, 236, 238-242] studies incorporated into this analysis. There are 4 other studies in Appendix 1.^[148, 150, 229, 243]

Specific Inhalational Challenge Testing

Specific inhalation challenge (SIC), also called specific bronchial provocation test (SBPT), is performed by generating an exposure to the suspect asthmagen that simulates workplace conditions, and following the subject's lung function for an asthmatic response. It is considered the ultimate "gold standard" for diagnosing sensitizer-induced OA, used when other methods have failed to establish the diagnosis;^[3, 7, 9, 12, 95, 113, 163, 164, 189, 192, 194, 244-254] or a reference standard as there is no other definitive diagnostic test.^[1] False negative results have been described if the wrong agent or dose challenge has been utilized or the sensitivity to an agent has decreased after long removal from exposure. However, this has been reported as a rare occurrence.^[255]

There are certain limitations to its use. The challenge system and equipment needed for generation of safe levels of exposure during specific inhalation challenge testing are complex and expensive.^[3, 6, 7, 11, 28] Significant problems include limited availability of test facilities and infrequent though potentially serious adverse effects.^[256, 257] There is little standardization in the method for generation and measurement of inhalation challenge material. Methods for performing diisocyanate challenges have varied from small open air rooms where the worker performs the task suspected of causing symptoms, to a closed circuit apparatus that generates vapor by blowing humidified air over the chemical contained in a flask residing in a silicon bath.^[151, 250] This technique offers distinct advantages over challenge rooms, in which wide variations in ambient diisocyanate concentrations may result in exposures above the TLVs. Due to better control of diisocyanate exposures, this method will trigger less exaggerated bronchoconstriction.^[76] Although adverse effects are less frequent than in the uncontrolled work challenge to

diisocyanates,^[256, 258-260] the safer closed circuit method is performed in few centers and is unavailable for most patients suspected of having diisocyanate or other sensitizer-induced asthma.

Specific Inhalational Challenge Testing for Diagnosing Work-Related Asthma

Specific inhalation challenge testing is recommended for use in diagnosing occupational asthma (OA) with latency for highly select cases, where the diagnosis of OA is highly suspected but has not been established by less invasive means. This testing should only be performed in appropriately equipped facilities, with direct medical supervision throughout the testing. For this reason, the recommendation is at level “C” despite the table of evidence; see below for full rationale.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Moderate

Performance – These tests may have serious complications that include fatalities. There are few centers that can safely and accurately perform these tests, and they should have the proper equipment and training.^[56] Asthmagen exposure should be done after a control day where the patient is not exposed to the suspected sensitizer and lung function is monitored for stability. The testing may be performed once, but may need to be repeated on another day or with a higher dose to identify positive responses.^[7] Patients should stop using short-acting beta 2-agonist agents 8 hours before testing and longer-acting medications 24 hours before testing.^[119] Positive responses, defined as a 20% fall in the FEV₁, may present in an immediate pattern (within 30 minutes of the exposure), which is typical for HMW agents, whereas a delayed pattern (2-8 hours after the exposure) is typical for LMW agents; a dual pattern demonstrating both early and late responses may be present with both LMW and some HMW agents.^[261] The full method and criteria for positivity of specific inhalation challenges with diisocyanates may be further reviewed elsewhere.^[262]

Indications – Most patients with suspected sensitizer-induced OA do not require this test, as their OA can be diagnosed with less invasive means.^[7, 249] The indications for specific inhalation challenge (SIC) include: 1) evaluation of a worker who has left the workplace and is unable or unwilling to return to work utilizing serial measurements of lung function; 2) initial documentation of a new cause of OA; 3) identification of a specific causative agent when there is work exposure to multiple substances;^[7, 254] or 4) confirmation of the diagnosis of OA and identification of causative agent, when other objective methods are not feasible, are less efficient, or have failed to provide definitive results.^[263]

Harms – Excessive bronchoconstriction and exacerbation of asthma; infrequently systemic and anaphylactic reactions.^[263]

Benefits – Accurate diagnosis facilitates management of OA.

Advantages and Limitations – Specific bronchoprovocation testing is not considered necessary in a worker with a history of OA in whom work-related airway obstruction is confirmed in association with exposure to an agent known to cause OA, or when the worker has been shown to be sensitized to that agent.^[264, 265] A specific inhalation challenge (SIC) test should not be used for the sole purpose of settling medico-legal issues.^[204] Limitations to the validity of the SIC include: 1) the challenge exposure does not replicate the work exposure; 2) the OA is caused by a mixture of agents, and not one single agent; 3) the worker has been out of exposure for too long, and has lost immediate reactivity to the agent; 4) the patient has unstable asthma with variations in airflow independent of exposure.

Rationale for Recommendation

There are numerous high- and moderate-quality studies evaluating the use of specific inhalational challenge testing as a confirmatory test for the diagnosis of occupational asthma.^[8, 54, 58, 69, 118, 119, 130, 146, 151-157, 180, 192, 204, 218, 226, 245-248, 254, 266-277] Specific inhalational challenge testing is expensive, time consuming, requires specialized sophisticated equipment, and has a considerably higher potential for adverse events than other diagnostic testing. While there are strongly supportive research studies that have been published suggesting level (A) recommendation, the major limitations and complications warrant downgrading to a recommended (C). SIC is recommended only for highly select cases, particularly where assurance of an accurate diagnosis is important.^[190]

Evidence for the Use of Specific Inhalation Challenge Testing (SIC)

There are 4 high-quality^[146, 151, 153, 216] and 16 moderate-quality^[58, 76, 155, 156, 218, 247-249, 254, 267, 274, 278-282] studies incorporated into this analysis. There are 12 other studies in Appendix 1.^[152, 154, 164, 226, 244-246, 250, 275, 276, 283, 284]

Nitric Oxide (Fractional Exhaled Nitric Oxide, FENO)

Nitric oxide (NO) is recognized as a biological mediator in humans.^[285] Measurement of total exhaled nitric oxide (FENO) is a test used for detection of endogenous inflammatory signals in childhood and adult asthmatics.^[270, 286-292] FENO is acknowledged to assess pathological rather than physiological changes in asthma.^[293] Increased nitric oxide in asthmatic airways is associated with up-regulation of inducible nitric oxide synthase as well as nitrite protonation in the acid environment of inflamed airways. The fraction of nitric oxide in expired air increases with uncontrolled asthma and decreases with anti-inflammatory therapy. FENO is considered to be a surrogate marker of eosinophilic inflammation in asthma.^[287] FENO is reportedly directly related to eosinophil activity suggesting other conditions such as eosinophilic bronchiolitis will affect FENO independent of asthma status.^[285, 293-296] Other factors such as smoking (generally lower), use of inhaled steroids (lower), exercise (lower), height (increase), gender (higher in males), atopy (increase), recent pulmonary infections (higher), ambient air levels of NO, and other pulmonary function testing (lower) may alter FENO results.^[293, 297-300] These factors, if not well described or controlled, can make it difficult to compare diagnostic studies.^[293] A more complete list of factors that may influence FENO follows, although there is not always agreement between studies as to the direction of change. Conditions in which FENO may be increased include allergic rhinitis and eczema (atopy), cough, chronic bronchitis, COPD, airway viral illness, a nitrate-rich diet, systemic sclerosis, and exercise-induced bronchoconstriction.^[285] Reductions (or reductions mixed with studies showing no change) in FENO have been reported for alcohol use, altitude, congestive heart failure, obesity, pulmonary hypertension, and spirometry.^[285] Smoking (active, passive, and cessation), caffeine, and cystic fibrosis have been reported to show both increases and decreases.^[285]

Exhaled Nitric Oxide Testing for Diagnosing Work-Related Asthma

Nitric oxide testing is not recommended for the diagnosis of OA, as it cannot differentiate between OA and other eosinophilic lung inflammatory conditions.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)
Level of Confidence – High

Exhaled Nitric Oxide Testing When More Objective Evidence is Needed

Exhaled nitric oxide testing is recommended for establishing a diagnosis of asthma when more objective evidence is needed, such as in litigated cases.

Strength of Evidence – Recommended, Evidence (C)
Level of Confidence – High

Exhaled Nitric Oxide Testing for Selective Monitoring of Asthma

Exhaled nitric oxide testing is moderately recommended for selective use in monitoring airway inflammation in patients with moderate and severe asthma.^[289, 301, 302]

Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – Moderate

Performed – Recommended for the select assessment of those with moderate to severe asthma to monitor treatment and control if strict protocols are in place and the physiology of the nitric oxide testing is well understood both by the examiner and the clinician interpreting the test. There are several inflammatory phenotypes in asthma and determination of the subtype is important in understanding the results and usefulness of FENO as a test.^[285]

Criteria and Standards for Use – Use criteria and standards as described in the ATS 2011 statement for the Interpretation of Exhaled Nitric Oxide Levels for Clinical Applications.^[285]

Indications – Monitoring airway inflammation. It may be of assistance in corroborating a diagnosis in patients with moderate to severe asthma when more objective measures are needed. It should not be used during acute asthma exacerbations.^[303] FENO is reported to be more accurate in patients with more inflammatory airway disease and therefore more effective in some patients than others.^[285, 289, 301] Normative values are still being developed.^[293, 297, 304-306] One review article opined that a single diagnostic measurement of 35 ppb or greater in a symptomatic individual should be considered clinically significant.^[293] ATS recommends that FENO values greater than 50 ppb be used to indicate that eosinophilic inflammation is present.^[285] Exhaled nitric oxide may also be used for sequential measurements to monitor asthma control. Studies suggest that a change of 20% in the value between visits is clinically significant.^[285, 293, 307] Optimum flow rates have been reported to be 50 mL/s.^[293]

Timing and Frequency of Testing – When changing therapy, it is recommended that FENO be measured every 2-4 weeks while the treatment plan is being modified and finalized.

Harms – None.

Benefits – Provides an objective index of airway inflammation that is minimally effort-dependent.

Advantages and Limitations – FENO is noninvasive and has been reported to be moderately effective in the monitoring of asthma.^[308, 309]

Rationale for Recommendations

The limitation of FENO in the diagnosis of asthma includes the heterogeneity of asthma causes and subtypes. While eosinophilic airway inflammation is common, it is not always the process in asthma (i.e., neutrophilic airway inflammation). Similarly, in patients already treated with steroids, the test may be falsely negative.^[285] Thus, the importance of FENO lies in its potential to identify steroid responsiveness rather than the diagnosis of asthma.^[285, 293, 301, 302] However, in certain circumstances, such as in litigation, where effort on spirometry can be in question, FENO can be used to support the diagnosis of asthma where more objective evidence is needed.^[285]

The sensitivity and specificity of FENO have not been sufficiently assessed for the diagnosis of OA. There are not any occupational allergens that have had investigational studies performed regarding FENO with determination of acceptable sensitivity, specificity, positive predictive value, and negative predictive value. However, there are multiple moderate-quality and a few high-quality studies of FENO for testing a variety of non-occupational asthmatic patients ranging from potentially mild cases to refractory asthmatic cases. One moderate-quality study assessed steroid-naïve patients and reported a sensitivity of 85% and a specificity of 90% for the diagnosis of asthma.^[310] Another study reported sensitivity of 88%.^[98] A study of steroid-naïve patients reported a sensitivity of 72.2% and specificity of 70.6% for the diagnosis of asthma compared to spirometry.^[311] Fortuna et al. reported a sensitivity of 77% and specificity of 64% in asthma patients.^[312] Kostikas reported a sensitivity of 52% and specificity of 85% when comparing young patients diagnosed with asthma to all other patients.^[299] Another study concluded that FENO is not likely to be beneficial in clinical measurement except in steroid-naïve patients.^[294] Demange et al. reported a sensitivity of 80% and specificity of 42% in detecting patients with airway hyper-responsiveness confirmed by methacholine challenge testing.^[304]

FENO is not invasive, has few adverse effects, but is moderate to high cost when used repeatedly. It is recommended for select use in moderate to severe asthma for monitoring response to asthma treatments. It is believed that controlling asthma will decrease lung inflammation, therefore decreasing the FENO levels with repeated testing.

Evidence for the Use of Nitric Oxide Testing

There are 2 high-quality^[309, 310] and 20 moderate-quality^[98, 158, 159, 270, 286, 287, 289, 292, 294, 296, 299, 301, 302, 304, 305, 308, 312-315] studies incorporated into this analysis. There are 4 low-quality studies in Appendix 1.^[288, 291, 300, 315]

Nasal Lavage

Nasal lavage, following nasal provocation testing, is used to assess occupational airway sensitization and allergic reactions.^[316-319] In nasal lavage, the cellular and biochemical findings in the nasal lavage fluid are analyzed for evidence of allergic reaction, including changes in the percentage of eosinophils, neutrophils, eosinophilic cationic protein (ECP), mast-cell tryptase, etc. before and after nasal provocation testing. The technique may differentiate allergic from non-allergic reactions, but it does not distinguish allergic manifestations of rhinitis from asthma.

Nasal Lavage Fluid Testing for Diagnosing Work-Related Asthma

Nasal lavage fluid analysis after challenge with the allergen is not recommended for the diagnosis of OA.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Moderate

Nasal Lavage Fluid Testing for Specific Allergen Testing and Monitoring of Symptomatic Workers

Nasal lavage is recommended for select workers with symptoms consistent with occupational airways allergy to specific allergens. Those specific allergens should have been evaluated in quality studies with reported specificity and sensitivity.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Moderate

Performed – Testing location needs to be experienced and properly trained in technique and have cell analysis capabilities.

Criteria and Standards for Use – The use of nasal lavage in clinical practice is still limited due to great interindividual variability and the lack of a standardized and validated method. Inflammatory cells, protein content and mediators can be measured in nasal lavage washings, but normative values have not been established. The types of mediators measured are not standardized but frequently include eosinophil cationic protein and mast-cell tryptase. Nasal secretions can be collected and weighed for quantifying the secretory activity, especially after allergen challenges.

Indications – To be used for allergens that have had investigational studies performed with acceptable sensitivity, specificity, positive predictive value, and negative predictive value. Allergens having met these criteria are animal allergens,^[320] flour,^[218, 269] chloramines,^[266] latex,^[267] and glutaraldehyde.^[226] Garbage workers have also been studied.^[272]

Timing and Frequency of Testing – The timing and frequency of testing has not been established. Nasal lavage is more useful in situations where subjects serve as their own controls as it occurs during nasal provocation testing or exposure at the workplace.

Harms – Minimal discomfort and minimal risk of coughing due to fluid aspiration.

Benefits – Sampling of relevant tissue for demonstration of specific allergic response.

Advantages and Limitations – Nasal lavage fluid testing is minimally invasive, has low adverse events, and may be high cost depending on frequency of testing. The test results do not diagnose OA but may indicate occupational airway allergy.

Rationale for Recommendations

There are seven moderate-quality studies that evaluated nasal lavage fluid in comparison to spirometry, skin prick testing, IgE testing and peak expiratory flow rates.^[218, 226, 266, 267, 269, 272, 320] Studies have reported significant increases in eosinophils, basophils, cytokines, and eosinophil cationic protein in patients with occupational allergies after challenge testing. They have also reported decreased spirometric FEV₁ values. These findings may assist with the diagnosis of OA; however, they cannot provide definitive evidence to confirm a suspected diagnosis. It is recommended for select, specific cases where there is known sensitivity and specificity and those results are reliable.

Evidence for the Use of Nasal Lavage

There are 8 moderate-quality studies incorporated into this analysis.^[218, 226, 266, 267, 269, 272, 273, 320]

Treatment Approach

The medical management of work-related asthma and outcome of interventions following a confirmed diagnosis may depend on several factors, including the worker's age and the causative agent. Early diagnosis and early avoidance of further exposure, either by relocation of the worker or substitution of the hazard, offer the best chance of complete recovery. Patients with sensitizer-induced occupational asthma (OA) should be removed from further exposure to the causative agent in addition to providing other asthma management.^[7] If medical removal is not possible, exposure should be minimized to as low as possible by means of worker relocation. Relocated workers should have increased health surveillance to demonstrate the absence of worsening of disease.^[56, 392] Determining the most effective treatment for WRA requires having precise information on the effect of different management options on clinical, physiological, and socioeconomic outcomes. However, the evidence that can be derived from current data has been limited by methodological weaknesses.^[393] There are very few articles that meet the methodologic quality of a randomized controlled trial or prospective cohort study, thus the recommendations regarding management of WRA are made on the basis of consensus due to insufficient evidence.

Management of Irritant-Induced OA

After acute inhalation of a respiratory irritant, acute airway responses should be assessed early and may require supplemental oxygen, bronchodilators, and corticosteroids. Although there is little objective evidence for the effectiveness for systemic corticosteroid therapy, this is often used for treatment in the hope of limiting airway inflammation.^[396] In individuals with subsequent irritant-induced asthma or WEA, optimizing asthma treatment and reducing the exposure to relevant workplace triggers has been recommended.^[7] If not successful, change to a workplace with fewer triggers is suggested in order to control asthma. Limited data exist on the effect of the cessation of exposure in patients with irritant-induced OA. One report of three patients with repetitive exposure to irritants at work suggested a benefit for removal from the exposure.^[397] Improvement in symptoms, though not always NSBHR was found in aluminum potroom workers after cessation of exposure.^[398, 399] Unlike workers with sensitizer-induced OA, workers with irritant-induced OA may be able to continue in their usual jobs if the risk of a similar high-level exposure to the inciting irritant substance is diminished via engineering controls and similar means are employed to prevent subsequent WEA, including the appropriate use of respiratory protective devices. The rationale for this approach is based on the unproven assumption that irritant-induced airway inflammation in patients with irritant-induced OA will diminish with a reduction of exposure that is analogous to what may occur in patients with occupational or tobacco smoke-related chronic bronchitis with a reduction in exposure.^[7]

Management of WEA

The literature on the natural history and management of patients with WEA is limited, and the factors that predict outcome are not well defined. The few studies completed to date have significant methodologic weaknesses and evaluated different treatment or preventive strategies in WEA patients.^[7] The goal of treatment is to minimize asthma exacerbations by reducing work exposures (e.g., by limiting sources of exposure, improving ventilation) and optimizing standard medical management with nonwork environmental control measures and pharmacologic treatment. The patient may be able to stay at the same job with reduced exposures, depending on the severity of asthma and extent of exacerbating factors at work, but a job change to a workplace with fewer triggers may be necessary if this approach fails to adequately prevent work-related exacerbation of symptoms.^[17] When a WEA case can no longer tolerate a work setting, the clinician and patient should carefully balance the potential benefit of removal from work with the benefits (financial and psychological) of continued working.^[400] Workers with work-exacerbated asthma had reduced airway inflammation and improved quality of life after the implementation of smoke-free environment legislation.^[401]

Management of Sensitizer-Induced OA

Following the diagnosis of sensitizer-induced OA, management decisions can be complex. For example, while complete avoidance of the sensitizer may be advisable, alternative employment is often not available or feasible, symptoms may initially be mild, and therapy may alleviate symptoms sufficiently to consider continued employment. This section summarizes the evidence available for the management of sensitizer-induced OA.

Prevention and Exposure Control

It has been stated that "all work-related asthma is potentially preventable through a tiered strategy of primary, secondary and tertiary prevention."^[7] Workplace exposure is considered primary prevention and consists of

engineering controls, administrative controls, and personal protective equipment (PPE). Engineering controls involve eliminating the potential exposure without any need for the employees to participate. Administrative controls, such as work practices, involve processes to minimize exposure. Personal protective equipment (PPE) relies on the employees' use to decrease exposure.^[321] Prevention strategies should also include educational information regarding the risk of sensitization disorders, the importance of exposure control measures, indicators of work-related asthma, and the steps to take if asthma symptoms occur in relationship to work exposures.^[322]

Exposure limits have been set by various bodies, including the American Conference of Governmental Industrial Hygienists (ACGIH) and the German MAK Commission. Control of exposure can be achieved by different measures; a hierarchical strategy is commonly applied (see Table 4. Hierarchy of Control Measures for Airborne Contaminants in the Work Environment in Order of Priority and Preference).^[321]

Table 4. Hierarchy of Control Measures for Airborne Contaminants in the Work Environment in Order of Priority and Preference

Elimination

- Total substitution of agent
- Different process
- Layout changes to work environment
- Adjust work practices: automation, robotization, remote control

Reduction

- Partial substitution of agent, change of form
- Adjustment to process, preventive maintenance, specialized appliance
- Good housekeeping in work environment
- Work practices: correct work procedures, training/instruction, motivation, supervision

Isolation

- Enclosure segregation
- Changes to working environment: glove box, safety cabinet, segregation, high-exposure departments
- Ensure enclosure of process hazards

Ventilation

- Local exhaust, ventilation, push/pull ventilation
- Changes to work environment: dilution ventilation, air douches, air curtains
- Work practices: portable jets, low-volume, high-velocity tools

Exposure Avoidance

- Changes to work environment: booths for operators
- Work practices: shorter shifts, fewer people, adjustment of work schedules

Personal Protection

- Work practices: respiratory protection, gloves, clothing

Adapted from Heederik D, Henneberger PK, Redlich CA. Primary prevention: exposure reduction, skin exposure and respiratory protection. *Eur Respir Rev.* 2012;21(124):112-24.

Substitution of an agent, for instance, can include substitution of enzymes with strong sensitizing potential by less strong sensitizing enzymes, or a change to a process that does not require the use of enzymes at all. When substitution is not possible, exposure reduction is the next best approach. Engineering controls can include isolation and enclosure to prevent inhalation of any possible irritants, or substituting a new agent that is less sensitizing.^[1] Exposure reduction can be achieved by reducing the source strength (i.e., amount or concentration emitted), modifying the formulation of the active ingredient (e.g., liquid or granule instead of powder), changing the process, or by improving general hygiene (good housekeeping). Other options are isolation of the source (enclosure or segregation), ventilation, avoidance of exposure, and use of PPE. Administrative controls can include limiting time in certain areas of the plant to decrease the amount of exposure and use of PPE and respirators. Often, optimal exposure reduction strategies consist of a combination of technical and organizational measures. In practice, exposure reduction relies on a combination of different interventions.^[321]

The relationship between the level of exposure to allergens and the occurrence of sensitization or work-related asthma has been studied for detergent enzymes,^[323-328] baking operations,^[329-335] wood dusts,^[336] platinum salts,^[230, 236] laboratory animals,^[203, 337-340] anhydrides,^[341, 342] diisocyanates,^[343-345] and shellfish.^[346, 347] Exposure response relationships indicate that implementation of primary preventive measures in the workplace that result in a reduction of exposure should also lead to a reduction in sensitization rate. However, the effect of exposure reduction measures has not been frequently studied in practice. Thus, relatively little is known about the effectiveness and efficacy of many possible exposure reduction measures.

The most convincing example of the beneficial effects of an exposure intervention is exposure to latex allergens. For natural rubber latex (NRL), a meta-analysis is available reviewing several studies that explored differences in exposure levels between health care workers using powdered and non-powdered gloves.^[348] The most powerful study investigating the use of non-powdered gloves, which was associated with lower exposure, was a longitudinal case crossover intervention. Substitution of powdered latex gloves with low-protein, powder-free NRL gloves or latex-free gloves greatly reduces NRL aeroallergens, NRL sensitization and NRL asthma in health care workers. None of the individual studies fulfilled strict criteria for good-quality intervention studies, i.e., they were observational studies without a randomized design. However, taken together, these studies support assertions that substitution of NRL greatly reduces NRL sensitization and asthma.

Fewer studies are available for asthma-inducing agents other than NRL. A modest increase in use of control measures and proper work practices has included the use of local exhaust ventilation and decreased use of compressed air. Studies have been undertaken with interventions comprising combinations of different preventive dust control measures, as well as education and PPE, for laboratory animals,^[349, 350] detergent enzymes,^[324, 351] anhydrides,^[352] diisocyanates,^[353] and baking operations.^[98, 354]

Skin exposure to certain OA inducing agents may increase the risk of OA, despite the limited epidemiological studies to date primarily regarding diisocyanate exposure. The contribution of skin exposure to asthma risk probably varies greatly with different allergenic exposures, work processes and settings, as well as other factors than can alter skin barrier function. Elimination of exposure, the preferred approach to preventing OA, reduces all routes of exposure, including skin exposure. Concern that skin exposure to chemical allergens and even possibly to HMW protein allergens may increase asthma risk has arisen based on several lines of "evidence," including clinical experience and case reports, animal studies, and limited epidemiological findings.^[24, 355, 356] Indirect exposure by others to work areas where asthmagens are in use is also of concern.^[357]

Use of PPE, particularly respirators, is considered less effective than eliminating or minimizing exposures at the source or in the environment.^[358] The success of respiratory personal protection requires an ongoing commitment by employers and employees to the selection, cleaning, maintenance and storage of equipment, as well as training, fit testing, and medical monitoring of users. Respirators are best used as an interim measure while efforts to control exposures at the source or in the environment are being implemented, or when controls at these other levels are not possible. Respirators have often been used in conjunction with other control activities at the source and/or environmental level. Such comprehensive exposure control systems that include the use of respirators have been implemented for workers exposed to laboratory animals,^[350, 359-361] dusts and fumes in aluminum production,^[362] diisocyanates,^[363] and disinfectants.^[7, 364] Although success at prevention has been reported, it is not possible to determine the contribution made by respirators alone.

Statements from professional organizations have addressed use of respirators for primary prevention of work-related asthma. An expert panel convened by the American College of Chest Physicians (ACCP) produced a publication on the diagnosis and management of work-related asthma.^[7] This document advises primary prevention by controlling exposures to known workplace sensitizers and irritants, briefly citing a variety of methods, including respirators. The British Occupational Health Research Foundation (BOHRF) also developed guidelines for OA.^[56] Similar to the ACCP document, the BOHRF guidelines emphasize reducing airborne exposures to OA agents. The advice specific to respiratory protective equipment (RPE) was: "use of RPE reduces the incidence of, but does not completely prevent, OA."^[56] The European Respiratory Society has recently reviewed the topic and concluded that there is little direct evidence that use of respirators is effective for the primary prevention of OA. Elimination or minimization of exposures was considered to be more effective.^[321]

There are a few studies that directly test whether respirator use is associated with a decline in the onset of OA. In one study, automobile body shop employees who applied paints containing diisocyanates were approximately one-third as likely to have OA symptoms if they used a positive pressure respirator. However, a relatively small number of participants used this respirator and the finding was not statistically significant.^[365] A second study provided

evidence that inconsistent use of respiratory protection might have negative consequences. Specifically, diisocyanate-exposed workers at a wood products plant were at greater risk for new-onset asthma-like symptoms if they removed their respirators even briefly ($p = 0.05$).^[355] A more direct investigation of the value of respiratory protection for primary prevention was conducted among workers who were manufacturing an epoxy resin utilizing hexahydrophthalic anhydride (HHPA).^[366] Study participants were offered a choice of three different respirators: a disposable dust and mist respirator, a half-face organic vapor cartridge respirator, or a full-face organic vapor cartridge respirator. The highest annual incidence for asthma over the 7 years of follow-up was 2%, compared to approximately 10% that was observed in employees before the introduction of respirators. There was no statistically significant difference between respirators, but none of the workers who wore the full-face respirators developed OA, even those who worked in high-exposure jobs.

Medical Removal

Once a diagnosis of work-related asthma (WRA) is confirmed, the patient should be advised (preferably verbally and in writing) that the prognosis is improved by early and complete removal from exposure. Symptoms and functional impairment associated with WRA may persist for many years after avoidance of further exposure to the causative agent.^[56, 392] Persistence of exposure to the agent causing OA is more likely to be associated with the persistence of asthma and NSBHR, and an accelerated decline in FEV₁, compared with complete avoidance of exposure.^[393] The systematic review conducted by the AHRQ concluded that workers with WRA who remain exposed to the causal agent continue to experience stable or worsened asthma symptoms and tend to show a decrease in FEV₁ over time, as well as an increase in NSBHR.^[1] The consequences of persistent exposure were not specifically examined in the clinical practice guidelines issued by the British Occupational Health Research Foundation (BOHRF)^[56] and the American College of Chest Physicians (ACCP).^[7]

Exposure Control as Treatment

As stated in a Cochrane review regarding workplace interventions for the treatment of OA, “There is very low-quality evidence that removal from exposure improves asthma symptoms and lung function compared with continued exposure. Reducing exposure also improves symptoms, but seems not as effective as complete removal. However, removal from exposure is associated with an increased risk of unemployment, whereas reduction of exposure is not. The clinical benefit of removal from exposure or exposure reduction should be balanced against the increased risk of unemployment.”^[538] However, there is some case report and small cohort study literature that supports removal or reduction of exposure to the causative agent. Exposure reduction and/or removal has been recommended by others, including BOHRF,^[56] ACCP,^[7] and the European Respiratory Society (ERS).^[393]

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent.^[133, 251, 252, 363, 539-546] The consequences of persistent exposure to the causal agent are more frequent persistence of symptoms and decline in pulmonary function.^[123, 539, 540, 542, 547-549] Asthma symptoms persist in almost all patients who remain exposed, while one-third of those who avoided exposure recover from their asthma.^[393] Persistence of exposure was associated with a decrease in forced expiratory volume in 1 sec (FEV₁)^[123, 547] and an increase in NSBHR^[547] compared with cessation of exposure. Changes in FEV₁ have been investigated according to cessation or persistence of exposure to the sensitizing agent. Patients with OA caused by red cedar dust who continued to be exposed had a more rapid decline in FEV₁ than those who were removed.^[550] The rate of decline in FEV₁ before and after removal from exposure in individuals with OA (87% of the cohort due to LMW agents) was significantly greater before than after cessation of exposure. The rate of decline after removal from exposure is similar to that observed in healthy adults.^[406]

Redeployment to a low-exposure area is not always effective. Reduction of exposure to the causal agent can lead to improvement or resolution of symptoms and NSBHR, although the limited available evidence indicates that this approach is less beneficial than cessation of exposure.^[393, 543, 551, 552] The AHRQ systematic review^[1] analyzed the outcome of symptoms,^[251, 252, 398, 539, 540, 553-557] asthma medications,^[251, 252, 539, 553, 554, 558] FEV₁, and NSBHR^[251, 252, 539, 553] after the reduction of exposure in studies published up to 2004. The review concluded that the data documented some improvement in asthma symptoms; no clear pattern of changes in medication use; an improvement in FEV₁ over time in less than half of the studies; and provided insufficient data (improvement in one of three studies) to draw conclusions about the changes in NSBHR. The guidelines of the BOHRF and ACCP stated that reduction of exposure “is not always effective”^[56] and that “there is little evidence for using this approach.”^[7] If workers are redeployed, exposure should be minimized to as low as possible by means of worker relocation. Relocated workers should have increased health surveillance to demonstrate the absence of worsening of disease.^[367]

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to avoidance of exposure.^[539, 542, 543, 559-562] A meta-analysis^[563] regarding asthma outcomes (i.e., improvement, recovery, and worsening of asthma symptoms and NSBHR) compared subjects who reduced exposure to the causal agent with those who completely avoided exposure. The most commonly identified causal agents, in seven out of 10 publications, were LMW agents, including isocyanates,^[363, 539, 564] colophony,^[251, 252] red cedar dust,^[547] platinum salts,^[540] and persulfate salts.^[565] Two studies involved a single HMW agent, NRL,^[553, 566] and one study evaluated patients with OA caused by various agents, of which 90% were LMW agents.^[548] The meta-analysis of pooled data showed that a reduction of exposure was associated with a lower likelihood of improvement and recovery of asthma symptoms and a higher risk of worsening of the symptoms and NSBHR compared with complete avoidance of exposure.^[563]

Patients should be informed of the possible adverse health effects of continuing exposure to themselves and to co-workers should they not permit necessary workplace investigations. Communicating with the workplace is useful, but requires the patient's written consent.^[392] Employers and their health and safety personnel should ensure that measures are taken to ensure that workers diagnosed as having OA avoid further exposure to its cause in the workplace.

Respiratory personal protective equipment (RPPE) can result in an improvement – but not complete elimination – of respiratory symptoms and airway obstruction in the short term.^[56, 393] Studies investigating the effectiveness of RPPE in those with OA are limited to small studies in provocation chambers or limited case reports. Air-fed helmet respirators may improve or prevent symptoms in some but not all workers who continue to be exposed to the causative agent.^[363, 567-572] Use of RPPE led to a significant reduction in respiratory symptoms and changes in functional parameters during short-term exposures, but failed to provide complete protection. There was no protective effect in workers with more severe asthma or in those who used RPPE irregularly.^[571] The proportion of workers with OA induced by red cedar dust who used a twin-cartridge respirator and remained exposed to the causal agent was significantly higher among the group with stable asthma than among the group with a deterioration of asthma.^[58] None of these studies provide information on practical issues (e.g., compliance) that could result from the long-term use of RPPE. Individuals with asthma might have difficulty adapting to a dual cartridge half-face mask respirator due to increased inspiratory resistance resulting in increased respiratory cycle time.^[573]

An exception is isocyanate-induced OA. This requires removal from exposure, as there have been reported deaths in patients on medication and using respiratory protection.^[259, 574-578] Studies have found that “continued TDI exposure has been associated with increasingly persistent and severe respiratory symptoms.”^[345, 363, 539, 579] Several early investigators described a progression of symptoms with decreasing exposure-response intervals and increasing severity of bronchospasm.^[580, 581] In addition, a significant decline in FEV₁ was observed among subjects with TDI-induced asthma who remained on the job (average duration 27 months), whereas a modest improvement in FEV₁ was observed among those who left.^[579] Similar results were reported in another study.^[363] There have been several cases of fatal bronchospasm reported in persons diagnosed with or believed to have had TDI-induced asthma at the time of an exposure incident.^[575, 582] The earlier case report pertained to an automobile refinisher with TDI-induced asthma, who continued working with a two-component PUR paint and subsequently died during a severe asthma attack 6 years later.^[575] This person had used a bronchodilator and steroids for asthma control and reported using a respirator to reduce exposure.

Treatment Recommendations

Removal or Reduction of Exposure

Education on the Persistence of Exposure

It is recommended that patients, physicians, and employers be informed that persistence of exposure to the causal agent is likely to result in a deterioration of asthma symptoms and airway obstruction.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – High

Rationale: Persistence of exposure to the causal agent is likely to result in a deterioration of asthma symptoms and airway obstruction. Thus, it is recommended that education be provided on this point.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Persistence of exposure; asthma, occupational asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 223 articles in PubMed, 203 in Scopus, 29 in CINAHL, 57 in Cochrane Library, 9730 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 1 randomized trial and 2 systematic reviews met the inclusion criteria.

Avoidance of Exposure for the Management of Work-Related Asthma

It is recommended that patients and their physicians be aware that complete avoidance of exposure is associated with the highest probability of improvement, although it may not lead to a complete recovery from asthma.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale: The highest probability of improvement is provided by complete avoidance of exposure; however, this may not lead to complete recovery from asthma. Thus, the education of patients and their physicians is recommended on this important point.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: avoidance of exposure, removal of exposure, cessation of exposure, risk avoidance; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 119 articles in PubMed, 60 in Scopus, 8 in CINAHL, 0 in Cochrane Library, 4,170 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 0 randomized trials and 2 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Reduction of Exposure, Removal of Exposure; Occupational Asthma, Asthma, Occupational, Asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 115 articles in PubMed, 750 in Scopus, 19 in CINAHL, 57 in Cochrane Library, 8050 in Google Scholar, and 0 from other sources. We considered for inclusion 10 from PubMed, 0 from Scopus, 0 from

CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 15 articles considered for inclusion, 0 randomized trials and 1 systematic reviews met the inclusion criteria.

Reduction of Exposure to Low-Molecular-Weight Asthmagens for the Management of Sensitizer-Induced Asthma

Reduction of exposure is not recommended as a strategy for certain low-molecular-weight asthmagens (diisocyanates).

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

<i>Rationale:</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; thus, it is not recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Reduction of Exposure to Low Molecular Weight Asthmagens, Respiratory Protective Devices, Primary Prevention, Prevention and Control; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 0 articles in PubMed, 1 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 60 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

Reduction of Exposure for the Management of Sensitizer-Induced Asthma

Reducing exposure to the causal agent is NOT RECOMMENDED (I) as a strategy in the management of sensitizer-induced asthma, as available evidence indicates that many asthma cases will worsen with continued exposure. 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) in order 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 (see Table 5. Medical Removal Considerations), and the clinical judgment of the physician.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

<i>Rationale:</i>	Many asthma cases will worsen with continued exposure. Thus, reducing exposure to the causal agent is not recommended (I) as a strategy in the management of sensitizer-induced asthma. 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,
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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) in order 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 (see Table 5. Medical Removal Considerations), and the clinical judgment of the physician.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Reduction of Exposure; Occupational Asthma, Asthma, Occupational, Occupational Asthma, Management of Sensitizer-induced Asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 607 articles in PubMed, 120 in Scopus, 92 in CINAHL, 1 in Cochrane Library, 1140 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 7 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials and 10 systematic reviews met the inclusion criteria.

Reduction of Exposure for the Management of Irritant-Induced Asthma

For irritant-induced asthma, it is recommended that exposure reduction to the lowest levels possible and careful medical monitoring should be performed to ensure early identification of worsening asthma.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale:

For irritant-induced asthma, exposure reduction to the lowest levels possible and careful medical monitoring are recommended to be performed to ensure early identification of worsening asthma.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: asthma, management, irritant-induced asthma, irritants, reduction; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 80 articles in PubMed, 810 in Scopus, 32 in CINAHL, 2 in Cochrane Library, 721 in Google Scholar, and 6 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 6 from other sources. Of the 6 articles considered for inclusion, zero articles met the inclusion criteria.

TABLE 5. MEDICAL REMOVAL CONSIDERATIONS

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

*Workplace exposure is defined as follows:

- Low exposure: when regular airborne exposure to the causative agent is not expected.
- Moderate exposure: when airborne exposures at or below the level of the occupational exposure limit (OEL) of the causative agent are expected.
- High exposure: when airborne exposures above the level of the occupational exposure limit (OEL) of the causative agent are expected.
- The occupational exposure limit (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 (ACGIH) Threshold Limit Values (TLVs®).

**Severity is defined as per severity of asthma and asthma control, as defined in the Global Initiative for Asthma Guidelines.^[394]

- Severe OA: having abnormal FEV₁/FVC (<70%) and requiring use of high-dose inhaled corticosteroids and long-acting inhaled beta-agonists for symptom control.
- Moderately Severe OA: having abnormal FEV₁/FVC (<70%) and symptoms that are well-controlled with low dose inhaled corticosteroids and long-acting inhaled beta-agonists.
- Low Severity OA: having normal FEV₁ 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 chromones.

Respiratory Protective Devices for the Management of Work-Related Asthma

The use of respiratory protective devices is not recommended as a safe approach for managing work-related asthma, especially in the long term and in patients with severe asthma. It is also not recommended as a stand-alone intervention, but may be when used for mild cases in lower exposure settings, on short-term bases in conjunction with other efforts to reduce or eliminate exposure and conduct appropriate medical monitoring. Table 5 provides guidance. Evaluating the ability of the worker to wear a respirator as per OSHA 1919.134 standard and selection of appropriate respirator are essential.

Strength of Evidence – Not Recommended, Insufficient Evidence (I) - Severe asthma or moderately severe asthma in worksites with medium or high exposures
Level of Confidence – High

Strength of Evidence – Not Recommended, Insufficient Evidence (I) - Stand-alone intervention, mild, moderate severity

Rationale: The use of respiratory protective devices is not recommended as a safe approach for managing work-related asthma, especially in the long-term and in patients with severe asthma. It is also not recommended as a stand-alone intervention, but may be when used for mild cases in lower exposure settings, on short-term bases in conjunction with other efforts to reduce or eliminate exposure and conduct appropriate medical monitoring. Table 5 above provides guidance. Evaluating the ability of the worker to wear a respirator as per OSHA 1919.134 standard and selection of appropriate respirator are essential.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Respiratory Protective Devices, Respiratory Device, Nebulizer, Inhaler, CPAP machine, Ventilator, Respirator, Vaporizer; Occupational Asthma, Asthma, Occupational, Occupational Asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1677 articles in PubMed, 1111 in Scopus, 1635 in CINAHL, 491 in Cochrane Library, 2850 in Google Scholar, and 0 from other sources. We considered for inclusion 9 from PubMed, 7 from Scopus, 5 from CINAHL, 2 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 26 articles considered for inclusion, 13 randomized trials and 7 systematic reviews met the inclusion criteria.

Pharmacologic Treatment

The pharmacologic treatment of OA and WEA does not differ from the treatment of asthma that is not work related.^[7] It relies on a stepwise approach according to the severity of asthma and asthma control, as defined in the Global Initiative for Asthma Guidelines (see Table 6. Initial Therapy for Asthma).^{[394, 402][395]} Treatment for patients with a diagnosis of severe asthma has been recommended by the ATS/ERS but the recommendations did not exclude nor specifically address OA or WEA.^[403] The physician and the patient should discuss and create a written “asthma action plan.”

Asthma is considered to be well controlled when the patient has few or no symptoms, no activity limitations, and little or no need for short-acting bronchodilators. Nocturnal symptoms are especially important, and their presence indicates loss of control even when they are infrequent. Suboptimal asthma control is associated with use of a short-acting bronchodilator for symptom control ≥ 2 d/wk, not using an inhaled corticosteroid (or using it incorrectly), high levels of airway obstruction reversibility, irritant exposure, including cigarette smoke, sensitization to allergens, including food allergens and an elevated FENO while using an inhaled corticosteroid. Poor outcomes have been associated with low lung function (FEV1 <60% of the predicted value), 1 or more severe exacerbations in the preceding 12 months, chronic rhinosinusitis, major psychological or socioeconomic problems, obesity and a history of intubation or intensive care unit admission for asthma. Spirometry should be followed at diagnosis, after starting asthma treatment, after exacerbations, and periodically thereafter.

A basic framework for initiation of therapy and summary of available drug treatment options is provided in Table 6. The goal is to control symptoms, maintain patient activity levels, reduce the loss of lung function and diminish risk for adverse outcomes from exacerbations.

Table 6. Initial Therapy for Asthma

Symptoms	Future Risk of Poor Outcome or Exacerbation	Initial Therapy
Less than twice per month	None	SABA only

Symptoms	Future Risk of Poor Outcome or Exacerbation	Initial Therapy
Less than twice per month	Any	SABA plus low-dose ICS
At least twice per month	Any	SABA plus low-dose ICS
On most days	Any	Low-dose ICS/LABA or medium-dose ICS
Nighttime symptoms occur at least once per week, regardless of other symptoms or future risks	Any	Low-dose ICS/LABA or medium-dose ICS
Severe uncontrolled symptoms or exacerbation	Any	Oral corticosteroid and moderate-dose ICS/LABA

ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; SABA = short-acting beta-agonist. From King-Biggs MB. Asthma. *Ann Intern Med.* 2019;171:ITC49-ITC64. doi: <https://doi.org/10.7326/AITC201910010> [404]

Pharmacological management of patients with asthma should occur in conjunction with recommendations to avoid exposure to the causative agent.^[56, 367] There is currently evidence that treatment with inhaled corticosteroids is superior to inhaled beta-2-agonists to prevent exacerbations of asthma; however, there is not quality evidence regarding any inhaled agent altering the long-term deterioration of asthma in those who remain exposed to the agent causing OA.^[393] The methodological quality of the studies regarding OA is low, the sample sizes are small, and dissimilar populations and interventions have precluded meta-analytic synthesis.^[7]

There are very few studies that have specifically examined pharmacologic treatment in the management of OA. The effectiveness of anti-asthma medications in patients who remain exposed to the causal agent has not been specifically addressed in some of the previously published guidelines^[7, 56] or in the Agency for Healthcare Research and Quality (AHRQ) systematic review.^[1] The AHRQ review identified 10 controlled clinical trials specifically involving patients with sensitizer-induced OA, of which several were short-term trials examining acute effects on the response to SIC. There was no significant deterioration in any of the asthma outcomes compared with baseline values in 10 subjects with occupational asthma due to various agents who were treated with inhaled corticosteroids and long-acting b2-agonists over a 3-year period.^[405] In contrast, another study reported that the decline in FEV₁ before removal from exposure to agents causing occupational asthma was not affected by the use of inhaled corticosteroids.^[406] A pilot study used treatment with leukotriene inhibitors.^[407]

Anti-Asthma Medications as an Alternative to Environmental Interventions

Anti-asthma medications are not recommended as a reasonable alternative to environmental interventions, such as exposure reduction or medical removal.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale:

Anti-asthma medications are not recommended as a reasonable alternative to environmental interventions such as exposure reduction or medical removal.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: anti-asthma medication, medication, pharmacology, anti-asthma pharmacology, asthma pharmacology; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 12,710 articles in PubMed, 25,634 in Scopus, 756 in CINAHL, 0 in Cochrane Library, 3,389 in Google Scholar, and 0 from other sources. We considered for inclusion 5 from PubMed,

1 from Scopus, 5 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 15 articles considered for inclusion, 6 randomized trials and 0 systematic reviews met the inclusion criteria.

Pharmacological Treatment Strategies for the Management of Asthma

It is recommended that the pharmacological treatment of work-related asthma follow the GINA recommendations for asthma.^[395]

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Rationale:

Pharmacological treatment of work-related asthma is recommended to follow general recommendations for asthma found in the current GINA recommendations for treatment of asthma.^[395] These stepwise management strategies include:

1. Treat modifiable factors and co-morbidities.
2. Do not treat asthma solely with short-acting beta-agonists.
3. For mild, intermittent symptoms, use inhaled corticosteroids-formoterol on a symptomatic basis (Step 1). May use inhaled steroid alone as needed. Steroid-short acting beta-agonist is acceptable, but ICS-formoterol is preferable. Regular ICS or ICS-long-acting beta-agonist is an option.
4. Daily ICS use plus as-needed short-acting beta-agonist or, as needed, low-dose ICS-formoterol (Step 2)
5. Low-dose ICS–long-acting beta agonist plus short-acting beta agonist PRN or low-dose ICS-formoterol and short-acting beta agonist PRN (Step 3).
5. Low-dose ICS-formoterol plus short-term beta agonist or medium-dose ICS–long-acting beta agonist plus as needed short-term beta agonist (Step 4).

Biological medications include: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab (anti-IgE, anti-IL5, anti-IL5R, and anti-IL4R meds). It is not recommended that biological medications be used to manage asthma as first-, second-, or third-line treatments. They may have a limited role in the management of asthma resistant to multiple other traditional treatments, including ICS, beta-agonists, leukotriene modifiers, chromones, and anti-cholinergics.^[395]

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Pharmacotherapy, drug therapy, pharmacological treatment, pharmaceutical treatment, medical treatment, drug therapies, asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 8827 articles in PubMed, 69 in Scopus, 26247 in CINAHL, 0 in Cochrane Library, 84500 in Google Scholar, and 1 from other sources. We considered for inclusion 15 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 1 from other sources. Of the 23 articles considered for inclusion, 13 randomized trials and 7 systematic reviews met the inclusion criteria.

Inhaled Corticosteroids for the Management of Asthma

It is recommended that inhaled corticosteroids are used in the pharmacological treatment of work-related asthma.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Moderate

<i>Indications:</i>	Considered the primary medication for the management of asthma. Should be included for all patients, including those with mild asthma ^[395] .
<i>Benefits:</i>	Control of asthma, reduced inflammation, reduced risk of severe exacerbations ^[395]
<i>Harms:</i>	Cough, sore throat, thrush, hoarseness
<i>Frequency/Dose/Duration:</i>	Per manufacturer’s recommendations.
<i>Indications for Discontinuation:</i>	Resolution of the asthma to such as extent that an inhaler is not required.
<i>Rationale:</i>	GINA Guidelines advise it is beneficial to initiate early treatment with inhaled corticosteroids in those with sensitizer-induced OA in addition to removal from exposure, ^[7, 395] although there is insufficient evidence to support systematic treatment with high-dose inhaled corticosteroids. ^[393] The AHRQ systematic review ^[1] also noted that after treatment with steroids, most of the available studies documented an improvement in asthma symptoms and NSBHR, and an increase in mean FEV ₁ , although only a few reported complete resolution of symptoms in the majority of the subjects. Two randomized controlled trials assessed the effects of systematic treatment with inhaled corticosteroids in addition to cessation of exposure. Treatment with beclomethasone dipropionate (1 mg twice daily for 5 months) was associated with reduced NSBHR. ^[410] Beclomethasone dipropionate (1 mg daily) was associated with a significant, though minimal, improvement in symptoms, peak expiratory flow and quality of life but no change in specific responsiveness to the causative agent (diisocyanates). ^[411]
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Inhaled Corticosteroids, adrenal cortex hormones; occupational asthma, asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1827 articles in PubMed, 915 in Scopus, 440 in CINAHL, 842 in Cochrane Library, 5940 in Google Scholar, and 1 from other sources. We considered for inclusion 18 from PubMed, 5 from Scopus, 15 from CINAHL, 2 from Cochrane Library, 2 from Google Scholar, and 1 from other sources. Of the 42 articles considered for inclusion, 30 randomized trials and 13 systematic reviews met the inclusion criteria.

Immunotherapy for Sensitizer-Induced Asthma

Immunotherapy is a possible treatment option for patients with sensitizer-induced OA, but there is limited evidence to support its efficacy except under selected circumstances.^[412] Immunotherapy could 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.^[7] There is a lack of evidence-based information on the effectiveness and adverse effects of specific immunotherapy with high molecular weight occupational allergens.^[393] Immunotherapy for high molecular weight antigens should be most effective when it targets one allergen or a few allergens in the workplace that are linked clinically to disease, and it may have less effect when the worker is also sensitized to environmental allergens not included in the extract. Immunotherapy for OA due to LMW chemicals is untested because of concerns about toxicity and the unclear role of IgE-associated sensitization. Immunotherapy may be given by the standard subcutaneous route, where there is ample published literature for some non-occupational allergens, or by the sublingual route, for which there is less information about efficacy especially with occupational allergens.^[7] Systemic reactions to immunotherapy are less frequent with the sublingual approach.^[413]

There have been a limited number of studies of immunotherapy with HMW allergens of potential occupational relevance. These include natural rubber latex (NRL) for health care workers, venom from stinging insects for beekeepers, wheat for bakers, and grass or ragweed pollen for outdoor workers. Subcutaneous immunotherapy for exposure to NRL has been shown to be effective in reducing workplace symptoms, specific skin reactivity, and medication use,^[414, 415] but has not yet been shown to improve the clinical course of OA.^[178, 416] These studies documented an improvement in rhinoconjunctivitis symptoms and a reduction in skin reactivity to latex, but there was no clear improvement in asthma outcomes. In addition, latex immunotherapy resulted in frequent systemic adverse reactions. Sublingual NRL immunotherapy has similar effects,^[417] but anaphylaxis occurred with higher doses.^[418]

Specific occupations have characteristic challenges that may affect management. Hymenoptera venom allergy is an occupational hazard of beekeepers and other outdoor workers. Immunotherapy is highly effective and is indicated for those with sensitizer-induced OA associated with severe anaphylaxis^[419-423] who are at risk for future stings. A placebo-controlled, double-blind trial of subcutaneous immunotherapy with a flour extract in 30 bakers with occupational asthma demonstrated that the treated patients showed a significant decrease in subjective symptoms, NSBHR to methacholine, and skin sensitivity and specific immunoglobulin (Ig)E to wheat flour without any adverse reactions.^[424, 425] A later study demonstrated diminished symptoms and drug use in a cohort of bakers after similar treatment.^[426] No studies have evaluated the efficacy of immunotherapy for laboratory animal allergy in animal workers (e.g., researchers and veterinarians), compared to the many studies for pet allergy. In non-occupational environmental settings, immunotherapy has been shown to prevent progression from rhinitis to asthma, and thus has the potential ability to alter the natural history of the disease.^[427-429] Immunotherapy is not indicated to treat irritant-induced asthma.

Immunotherapy for the Management of Sensitizer-Induced Asthma

It is recommended that immunotherapy may be considered in settings where occupational asthma (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.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Rationale:

Immunotherapy is recommended to be considered in settings where occupational asthma 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.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Immunotherapy; occupational asthma, management of asthma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 602 articles in PubMed, 358 in Scopus, 27 in CINAHL, 134 in Cochrane Library, 2600 in Google Scholar, and 0 from other sources. We considered for inclusion 79 from PubMed, 5 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 90 articles considered for inclusion, 46 randomized trials and 37 systematic reviews met the inclusion criteria.

Prognosis

The long-term consequences of WRA are variable and require prolonged follow-up. Symptoms and functional impairment associated with WRA may persist for many years after avoidance of further exposure to the causative agent. Outcomes are best in those patients with a shorter duration of exposure after onset of symptoms.^[7] Evidence supports the view that WRA may become a chronic condition, similar to non-work-related asthma, and may require similar prolonged medical management.^[56, 392]

The symptoms and functional impairment of WRA, especially OA caused by various agents may persist for many years after avoidance of further exposure to the causative agent.^[133, 180, 255, 281, 363, 398, 539, 547, 549, 553, 560, 564, 579, 584-592] Improvement or resolution of symptoms or of preventing deterioration is more likely in workers who have:

- 1) no further exposure to the causative agent,^[133, 251, 252, 363, 539-542, 544-546]
- 2) relatively normal lung function at the time of diagnosis,^[133, 539, 549, 560, 561, 592, 593] and
- 3) shorter duration of symptoms prior to diagnosis.^[133, 363, 539, 542, 543, 559, 561, 562, 592]

The AHRQ review of sensitizer-induced OA demonstrated continued improvement of lung function, often requiring follow-up durations of more than 2 years.^[1] Prolonged follow-up has also been required to demonstrate improvement in nonspecific airway responsiveness. However, complete avoidance of exposure to the causal agent results in symptom recovery and resolution of NSBHR in less than one-third of affected workers.^[393] A systematic review of the outcome of sensitizer-induced OA reported a pooled estimate of symptomatic recovery of 32%, within a median duration of follow-up of 31 months. The pooled prevalence of persisting nonspecific bronchial hyperresponsiveness was 73% and was significantly greater for those with OA from HMW agents compared with those with OA from LMW agents.^[594] More recent studies published subsequently to the review by Rachiotis yielded similar estimated rates of symptomatic recovery and persistence of NSBHR.^[111, 170, 172, 173, 595, 596]

Improvement in NSBHR can continue for years after cessation of exposure, but the rate of improvement is steeper during the first 2.5 years.^[597] A determinant of improvement in NSBHR at follow-up has been found to be the severity of NSBHR at diagnosis.^[552] Induced sputum analysis has demonstrated that failure to improve NSBHR after cessation of exposure was associated with persistent airway inflammation,^[593, 598] but inflammation and airway remodelling may be present in subjects who have recovered from symptoms and NSBHR.^[111, 599] The long-term outcomes of acute irritant-induced asthma are thought to be no different.^[600] However, a cohort study of pulp mill workers found that irritant peak exposure during gassing episodes was a strong predictor of changing work due to respiratory problems, even after adjustment for asthma, chronic bronchitis, and chronic rhinitis.^[601]

Work-related asthma may become a chronic condition, similar to non-work-related asthma, and may require similar prolonged medical management. Patients with confirmed or possible OA should be followed up at a specialist center while risks of continuing exposure to allergen remain. The recommended follow-up is every 3 months for 1 year, and then every 6 months thereafter. Patients with confirmed OA who have left work, or who have no ongoing asthmagen exposure risk, should be followed up for a minimum of 3 years at a specialist center.^[56, 392] Patients with a diagnosis of OA should be followed with pulmonary function testing and nonspecific airway responsiveness testing (if available), unless asthma has cleared, regardless of their continued exposure status.^[7]

Employment Outcome

The risk of unemployment may^[602] or may not,^[603, 604] be higher than in other adult asthmatics and may fall with increasing time from diagnosis.^[559] Approximately one-third of workers with OA are unemployed up to six years after diagnosis.^[123, 553, 559, 591, 602-606] Workers with OA suffer financially.^[24, 123, 553, 602, 604, 605] Systems that incorporate retraining may be more effective than those that do not.^[605, 607]

One prospective study compared asthma severity, disease-related costs and work-derived income after cessation or persistence of exposure to various agents causing OA. Noticeably, the investigators did not clearly distinguish the persistence of exposure to the same conditions at work from a reduction of exposure to the causal agent, since 43% of the subjects with persistent exposure actually had intermittent or lower exposure.^[541] When compared with persistence of exposure to causal agents, complete avoidance resulted in a significant decrease in asthma severity and health care expenses, but also in work-derived income.^[541] Two publications reported on the socioeconomic outcomes of workers with occupational asthma caused by colophony^[251, 252] and NRL gloves. These studies revealed that the rate of unemployment was significantly higher among those who avoided exposure compared with those who reduced exposure. Among workers with latex-induced occupational asthma,^[553] a “major” loss of income

was more frequently reported by subjects who ceased exposure to latex than by those who remained exposed to reduced levels of latex. A recent case review found that continued employment in the same job 6 months after diagnosis of OA could not be predicted by FEV₁, gender, age, occupational status, exposure antigen, smoking habits, or duration of symptoms before diagnosis; only atopy was a prognostic factor.^[608]

Pulmonary rehabilitation may be effective even in the complex settings of occupational respiratory diseases, including asthma, providing sustained improvement of functional capacity, and reducing health care utilization.^[609] No studies have made direct comparisons between different systems of rehabilitation.⁽⁵⁶⁾

Specialty Care

The National Heart, Lung, and Blood Institute (NHLBI) has established the following guidelines for referral of adult patients to a medical specialist in asthma:^[5]

- Patient has had a life-threatening asthma exacerbation.
- Patient is not meeting the goals of asthma therapy after 3-6 months of treatment. An earlier referral or consultation is appropriate if the physician concludes that the patient is unresponsive to therapy.
- Signs and symptoms are atypical suggesting an alternative diagnosis.
- Other conditions complicate asthma or its diagnosis (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis, vocal cord dysfunction, gastroesophageal reflux disease, and COPD).
- Additional diagnostic testing is indicated (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy).
- Patient requires additional education and guidance on complications of therapy, problems with adherence, or allergen avoidance.
- Patient is being considered for immunotherapy.
- Patients that require more intense therapy in the stepwise algorithm for the management of asthma as per the NHLBI guidelines (NHLBI: Step 4 care or higher or step 3 for children 0-4 years of age. Consider referral if patient requires step 3 care or step 2 for children 0-4 years of age.)
- Patient has required more than two bursts of oral corticosteroids in 1 year or has an exacerbation requiring hospitalization.
- Patient requires confirmation of a history that suggests that an occupational or environmental inhalant or ingested substance is provoking or contributing to asthma.
- Depending on the complexities of diagnosis, treatment, or the intervention required in the work environment, it may be appropriate in some cases for the specialist to manage the patient over a period of time or to co-manage with the primary care physician.
- In addition, patients who have significant psychiatric, psychosocial, or family problems that interfere with their asthma therapy may need referral to an appropriate mental health professional for counseling or treatment. These problems have been shown to interfere with a patient's ability to adhere to treatment.

In general, cases of reversible airways obstruction suspected of being WRA should be referred to a specialist in occupational medicine in the following situations:

- The triggering condition or antigen is unknown and the patient continues to work in the environment.
- The worker is planning a return to work or change in jobs or assignment and requires counseling on future risk, accommodation, and fitness for duty.
- The pulmonary specialist in the case is unfamiliar with occupational exposures and the workplace.

Medical Surveillance

Medical surveillance is the systematic collection and analysis of health data from defined populations for the purpose of prevention and is considered secondary prevention by preventing advanced disease in exposed workers. There are generally three stages in the process: 1) data collection and analysis; 2) preventive interventions; and 3) evaluation. Medical surveillance is **not** the detailed diagnosis of an individual patient, epidemiologic research, individual case reporting, data collection without prevention benefit, or a substitute for exposure control. It is not hazard surveillance, in which exposure and processes are measured, nor is it biomonitoring, which in the context of WRA, is used to assess exposure to a few specific occupational asthmagens.

While engineering controls are the ideal solution for exposure control and primary prevention, they are often not possible due to technology, lack of substitutions, or cost. If there is any possibility of exposures to occupational asthmagens, a medical surveillance program is appropriate.^[7] Additionally, medical surveillance has been found beneficial by identifying work processes associated with incidence of occupational asthma.^[357] Multiple surveillance methods for WRA have been utilized, and the methods have varied by setting. The goal is to include all potentially exposed workers in a health surveillance program that can be effective for secondary prevention, the early identification of WRA before permanent impairment occurs. A diagnosis of WRA (i.e., asthma caused by work) should not be made on the basis of history alone, but be supported by physiological and immunological investigations of proven diagnostic benefit.^[7, 56, 367] Following a validated diagnosis of WRA, especially OA physicians should recommend early avoidance of further exposure, because this offers the best chance of complete recovery. If appropriate and timely interventions are not taken, the prognosis of OA is poor, with only approximately one-third of workers achieving full symptomatic recovery.

Medical surveillance methods for early detection of OA in worker groups known to have sensitizer exposure in the workplace most frequently use a health questionnaire, spirometry, peak expiratory flow monitoring and, for specific asthmagens, antibody and skin prick testing, as recommended elsewhere in this guideline. The focus is to detect “possible” cases and then engage in diagnostic confirmation or exclusion by means of definitive clinical testing. The medical surveillance program may primarily be based on questionnaires but should also include lung function tests to document the temporal change in respiratory function and also identify non-symptomatic workers with respiratory changes consistent with a diagnosis of asthma. If there are positive findings, the individual should be referred to a physician having competence in assessment of OA so that the evaluation may proceed rapidly to confirm a diagnosis of occupational asthma before worker relocation. The process of objective confirmation of a diagnosis of OA should proceed immediately and rapidly on reasonable suspicion that OA may have developed.^[56, 367]

Surveillance questionnaire items found to be most useful in identifying subjects with OA in surveillance programs were job title and duration of work under the same job title, and identification of products causing symptoms in order to define a process or a product responsible for the respiratory symptoms. The nature and timing of symptoms in relation to work, interval between onset of exposure at work and onset of symptoms, and the status of respiratory symptoms on working days as compared with days away from work (including weekends and vacations) is key. Persistence and timing of symptoms should be evaluated, including if they disappear or change.^[67, 368]

Questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for work-related asthma. Questionnaire items that distinguish OA confirmed by specific inhalation challenge from non-work-related asthma or symptoms not resulting from asthma were sensitive but non-specific and were more useful for high molecular weight agents than low molecular weight agents. Questionnaire alone would have found all individuals referred for further diagnostic evaluation (i.e., no spirometry benefit).^[369, 370] A change in questionnaire responses over time should lead to assessment of the interval between onset of symptoms and current questionnaire and interval between last occupational exposure and current questionnaire. Questionnaires need as much technical attention and skill as pulmonary function tests regarding content items, wording, and cultural relevance. They can be delivered on paper, on-line, assisted, interviewer and are subject to interpretation by the examiner, especially when reviewing sequential questionnaires over time.^[371]

Timing of the surveillance should be at least pre-placement, periodic (with the interval defined by consideration of the history of incidence in reported cases) and upon concern post exposure or onset of significant respiratory illness. Beyond a good questionnaire, WRA medical surveillance frequently includes spirometry. Antibody and skin prick testing may be part of the surveillance scheme for specific asthmagens, if the asthmagens meet criteria for use. Review by a well-qualified objective physician, with experience in the evaluation of WRA is important. Questionnaire answers suggestive of WRA, and significant decrement in FEV₁ and FVC beyond that predicted by age indicates that a confirmatory assessment be performed to confirm not only a diagnosis of asthma but also to establish whether temporal changes in pulmonary function correlate with symptoms in the workplace. The confirmatory assessment is essentially to diagnose or exclude the diagnosis of WRA, and recommended methods are as noted in the diagnosis section of this guideline. Serial peak expiratory flow monitoring may be used as part of the initial stages of the confirmatory assessment while the worker is in the workplace to objectively document correlation of loss of airflow with symptoms.^[372-380]

The early detection of cases of WRA should focus primarily on respiratory symptoms and any temporal relationship with work, as opposed to reliance upon spirometry. It requires a coordinated approach between occupational

health, primary care and secondary health care. There should be as few steps as possible between symptom detection and final diagnosis to diminish loss of initially identified cases to follow-up.^[381] Use of a two-step screening process, identifying work-related symptoms and presence of sensitization in general^[382, 383] or sensitization to work-related high molecular weight allergens,^[384] is the most efficient approach to identify potential cases of high molecular weight OA. For example, a strategy identifying bakers with sensitization to a work-related asthmagen (positive serological test against wheat flour or fungal α -amylase) and also reporting upper respiratory symptoms was the most effective strategy at identifying early stage baker's asthma, reducing exposures and improving outcomes.^[384] In another study of workers exposed to laboratory animal allergens, a two-step prediction rule based on work-related symptom reports, and positive skin prick tests indicating atopy, was able to accurately identify those workers to be subsequently evaluated by skin testing to lab animal allergens.^[382, 383]

One-time screening, as in cross-sectional studies, misses cases due to the low prevalence of OA, healthy worker effect, and selection bias (those affected select out of employment). But routine surveillance may underestimate cases without ongoing participation.^[385] Case loss is minimized by longitudinal study and follow-up as long as inception cohort is stable and no workers are lost to follow-up.^[386, 387] However, cases detected by one-time screening had less severe asthma than cases from pre-screening era, in cases confirmed by specific inhalation challenge, and had a better outcome at time of diagnosis and 2 years later.^[388]

State and federal surveillance programs such as NIOSH Sentinel Event Notification System for Occupational Risks (SENSOR) have limits as most cases are reported "without objective evidence" of asthma such as spirometry, serial peak expiratory or methacholine challenge being impractical, specific inhalation challenge being infeasible or unavailable. State reports of WRA are mainly from health care providers and are affected by practice variability.^[389] State reporting requirements are variable, and are often ignored. Voluntary physician reporting is frequently unreliable, unrepresentative, and not effective in prevention.^[390, 391]

A decline in the number of workers' compensation OA cases due to isocyanates has been noted in Ontario after surveillance for diisocyanates was introduced. OA from all causes was diagnosed earlier and indicators of severity of asthma were also milder. Although engineering and industrial hygiene measures may have contributed to these changes, the findings indicated a beneficial contribution from the medical surveillance program for workers exposed to diisocyanates. However, the reduction in the number of cases could not be directly attributed to the performance of medical surveillance alone.^[28]

Appendix 1: Low-quality/Supplementary Studies

The following low-quality/supplementary studies were reviewed by the Evidence-based Practice Asthma Panel to be all inclusive, but were not relied upon for purpose of developing this document's guidance because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.^[610]

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