CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF WORK-RELATED ASTHMA: ACCP CONSENSUS STATEMENT

Diagnosis and Management of Work-Related Asthma*

American College of Chest Physicians Consensus Statement

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Background: **A previous American College of Chest Physicians Consensus Statement on asthma in the workplace was published in 1995. The current Consensus Statement updates the previous one based on additional research that has been published since then, including findings relevant to preventive measures and work-exacerbated asthma (WEA).**

Methods: **A panel of experts, including allergists, pulmonologists, and occupational medicine physicians, was convened to develop this Consensus Document on the diagnosis and management of work-related asthma (WRA), based in part on a systematic review, that was performed by the University of Alberta/Capital Health Evidence-Based Practice and was supplemented by additional published studies to 2007.**

Results: **The Consensus Document defined WRA to include occupational asthma (*ie*, asthma induced by sensitizer or irritant work exposures) and WEA (*ie*, preexisting or concurrent asthma worsened by work factors). The Consensus Document focuses on the diagnosis and management of WRA (including diagnostic tests, and work and compensation issues), as well as preventive measures. WRA should be considered in all individuals with new-onset or worsening asthma, and a careful occupational history should be obtained. Diagnostic tests such as serial peak flow recordings, methacholine challenge tests, immunologic tests, and specific inhalation challenge tests (if available), can increase diagnostic certainty. Since the prognosis is better with early diagnosis and appropriate intervention, effective preventive measures for other workers with exposure should be addressed.**

Conclusions: **The substantial prevalence of WRA supports consideration of the diagnosis in all who present with new-onset or worsening asthma, followed by appropriate investigations and intervention including consideration of other exposed workers.** ***(CHEST 2008; 134:1S–41S)***

Key words: asthma; occupational lung; preventive medicine

Abbreviations: ACCP = American College of Chest Physicians; AHRQ = Agency for Healthcare Quality and Research; CE = cost effectiveness; EBC = exhaled breath condensate; ENO = exhaled nitric oxide; HHE = Health Hazard Evaluation; HMW = high molecular weight; HSA = human serum albumin; LMW = low molecular weight; MSDS = material safety data sheet; NIOSH = National Institute for Occupational Safety and Health; NPV = negative predictive value; NRL = natural rubber latex; OA = occupational asthma; OSHA = Occupational Safety and Health Administration; PC_{20} = provocative concentration causing a 20% fall in FEV_1; PEFR = peak expiratory flow recording; PPV = positive predictive value; RADS = reactive airways dysfunction syndrome; RAST = radioallergosorbent test; RCT = randomized controlled trial; SIC = specific inhalation challenge; SPT = skin prick test; VCD = vocal cord dysfunction; WEA = work-exacerbated asthma; WRA = work-related asthma

EXECUTIVE SUMMARY

This Consensus Statement on the diagnosis and management of work-related asthma (WRA) has been developed by an expert panel of specialists in allergy, pulmonary medicine, and occupational medicine, which was impaneled at the request of the American College of Chest Physicians (ACCP) Health and Science Policy Committee, with the endorsement of the ACCP Board of Regents to update the earlier 1995 ACCP Consensus Statement: Assessment of Asthma in the Workplace.[1] The initial aim was to develop formal recommendations using an evidence-based approach and including greater consideration of work-exacerbated asthma (WEA) than that in the previous Consensus Statement. However, by the nature of the topic, the citations captured through systematic review were limited in scope and number. Randomized controlled trials (RCTs) relevant to the diagnosis and treatment of WRA are not available and are not likely to be performed. A limited number of studies have compared various diagnostic tests for sensitizer-induced occupational asthma to the selected reference standard test, a specific inhalation challenge (SIC). Most of the published literature consists of clinical studies of patients in whom occupational asthma (OA) was diagnosed rather than cross-sectional or longitudinal cohort studies of exposed workers. The panel also considered additional studies, which were not included in the formal Agency for Healthcare

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As part of the practice of occupational pulmonary medicine, most of the panel members have served as consultants or medical experts in workers' compensation or other cases of suspected work-related asthma, and/or have provided other consulting services involving possible work-related asthma. In addition, Dr. Tarlo has received research funding for studies in work-related asthma from the Ontario Thoracic Society, and both Drs. Tarlo and Liss have received research funding from the Ontario Workplace Safety and Insurance Board Research Advisory Council for studies including work-related asthma. Dr. Tarlo has also served the following organizations with a direct interest in occupational asthma: the American Thoracic Society (Committee on Work-Exacerbated Asthma); the American Academy of Asthma, Allergy and Immunology Occupational Disease Committee; and the Canadian Thoracic Society Asthma Committee. Dr. Balmes has served organizations with a direct interest in occupational asthma, including the American Thoracic Society (Committee on Asthma Impairment and Committee on Occupational Contribution to the Burden of Obstructive Airway Disease) and the Centers for Disease Control and Prevention (CDC)-NIOSH (Study Section). Dr. Beckett has received funding from the Association for Occupational and Environmental Clinics and NIOSH to review the literature and provide written reports on issues related to occupational lung diseases, including occupational asthma. Dr. Beach has received research funding from the Alberta Workers' Compensation Board Research Program. Dr. Bernstein has received CDC-NIOSH research funding. Dr. Blanc has served organizations with a direct interest in occupational asthma, including the American Thoracic Society (Committee on Occupational Contribution to the Burden of Obstructive Airway Disease) and the Institute of Medicine committee reviewing respiratory disease programs at CDC-NIOSH. Dr. Brooks has received CDC-NIOSH research funding. Dr. Harber has served the following organizations with a direct interest in occupational asthma: the American College of Occupational and Environmental Medicine (Board of Directors, Pulmonary Committee, and Treatment Guidelines Committee); the American Thoracic Society (the Asthma Impairment Committee and the Committee on Work Exacerbated Asthma); the American Medical Association (guidelines reviewer); and CDC-NIOSH (the Committee on Work Exacerbated Asthma, Study Section). He has received research funding from CDC-NIOSH for projects related to the recognition and prevention of occupational lung diseases such as asthma. Dr. Lemiere has received research funds from the Institut de Recherche en Sante et Sécurité au Travail (or IRSST) Robert Sauve and from CDC-NIOSH, and is a member of the American Thoracic Society Committee on Work Exacerbated Asthma and Canadian Thoracic Society Asthma Committee. Dr. Pacheco has received research funding from the National Institutes of Health (NIH) for projects related to occupational asthma, and is also a member of the American Academy of Asthma, Allergy, and Immunology Occupational Disease Committee. Dr. Redlich has received research funding from the NIH and CDC-NIOSH for projects related to occupational asthma, and has also served organizations with a direct interest in occupational asthma, including the American Thoracic Society (Committee on Work Exacerbated Asthma), American Medical Association (guidelines reviewer) and CDC-NIOSH (grant reviewer). Dr. Rowe is supported by a 21st Century Research Chair from the Government of Canada (Ottawa, ON, Canada) and has received funding for work-related asthma research from the Agency for Healthcare Quality and Research (Bethesda, MD). Drs. Balkissoon, Cowl, and Daroowalla have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. None of the authors has received funding from tobacco companies.

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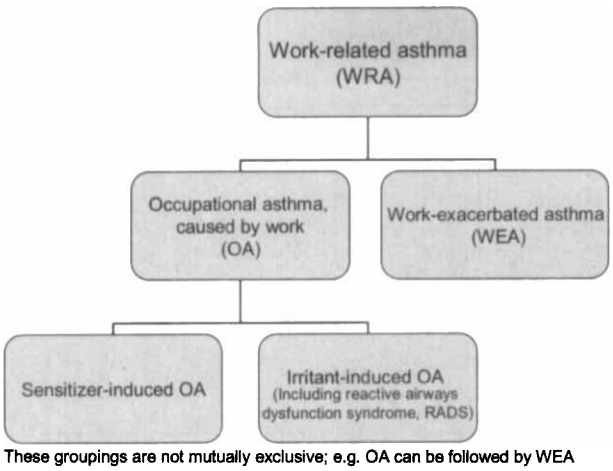

FIGURE 1. Relationships of asthma to the workplace.

Quality and Research (AHRQ) analysis, as well as later literature identified by an additional review of the literature into 2007. Therefore, due to the evidence considered for this document, this statement does not use the ACCP grading system (which relies heavily on RCT data),[2] but rather is based on the best available evidence and has been arrived at by consensus among the panel members. This Consensus Document addresses WRA (Fig 1), which the panel defined as including OA (caused by work) as well as WEA (preexisting or concurrent asthma that is worsened by work factors). In addition to addressing the diagnosis and management of patients with WRA, this Consensus Statement also covers several other important topics, including the physician's role in promoting safer employment options and access to worker's compensation or other benefit systems, as well as the prevention of WRA. It is hoped that this document will assist health-care providers in the diagnosis and management of WRA. The advised approach is summarized in Figure 2. Since WRA is potentially largely preventable and is best diagnosed early in its course, this Consensus Document also addresses primary, secondary, and tertiary preventive measures for WRA. Additional practical materials are provided on the *CHEST* Web site (www.chestjournal.org). Consistent with the ACCP requirements for consensus statements, the panel does not use the term *recommendation* but instead "suggests" approaches based on panel consensus in light of the best available evidence.

The panel reached consensus (organized around 12 main topics), on the following, as summarized below:

1. **In all individuals with new-onset or worsening asthma, take a history to screen for WRA (OA and WEA). Then confirm the diagnosis of asthma and investigate to determine whether the patient has WRA, performing these tests, whenever possible, prior to advising the patient to change jobs.**
2. **In all individuals with suspected WRA, obtain a history of job duties, exposures, industry, use of protective devices/equipment, and the presence of respiratory disease in coworkers, and consult material safety data sheets (MSDSs), which list many recognized hazardous agents. Document the onset and timing of symptoms, medication use, and lung function, and their temporal relationship to periods at and away from work.**
3. **In individuals who have asthma not caused by work but that subsequently worsens while working, consider the diagnosis of WEA, which is usually based on changes in symptoms, medication use, and/or lung function temporally related to work.**
4. **In individuals with suspected sensitizer-induced OA, in addition to carefully documenting the occupational history, perform additional objective tests when feasible (*eg*, serial peak flow recordings, serial methacholine challenges, immunologic assessments, induced sputum testing, and SICs) to improve the diagnostic probability.**
5. **In individuals with suspected WRA who are currently working at the job in question, record serial measurements of peak flow as part of the diagnostic evaluation and ask the patient to record these optimally a minimum of four times daily, for at least 2 weeks at work and 2 weeks off work.**
6. **In individuals with suspected sensitizer-induced OA, working at the job in question, perform a methacholine challenge test or obtain comparable measurements of nonspecific airway responsiveness during a working period, and repeat it during a period (optimally, at least 2 weeks) away from the work exposure to identify work-related changes.**
7. **In individuals with suspected sensitizer-induced OA, perform immunologic tests (skin prick testing or *in vitro* specific IgE assays) to identify sensitization to specific**

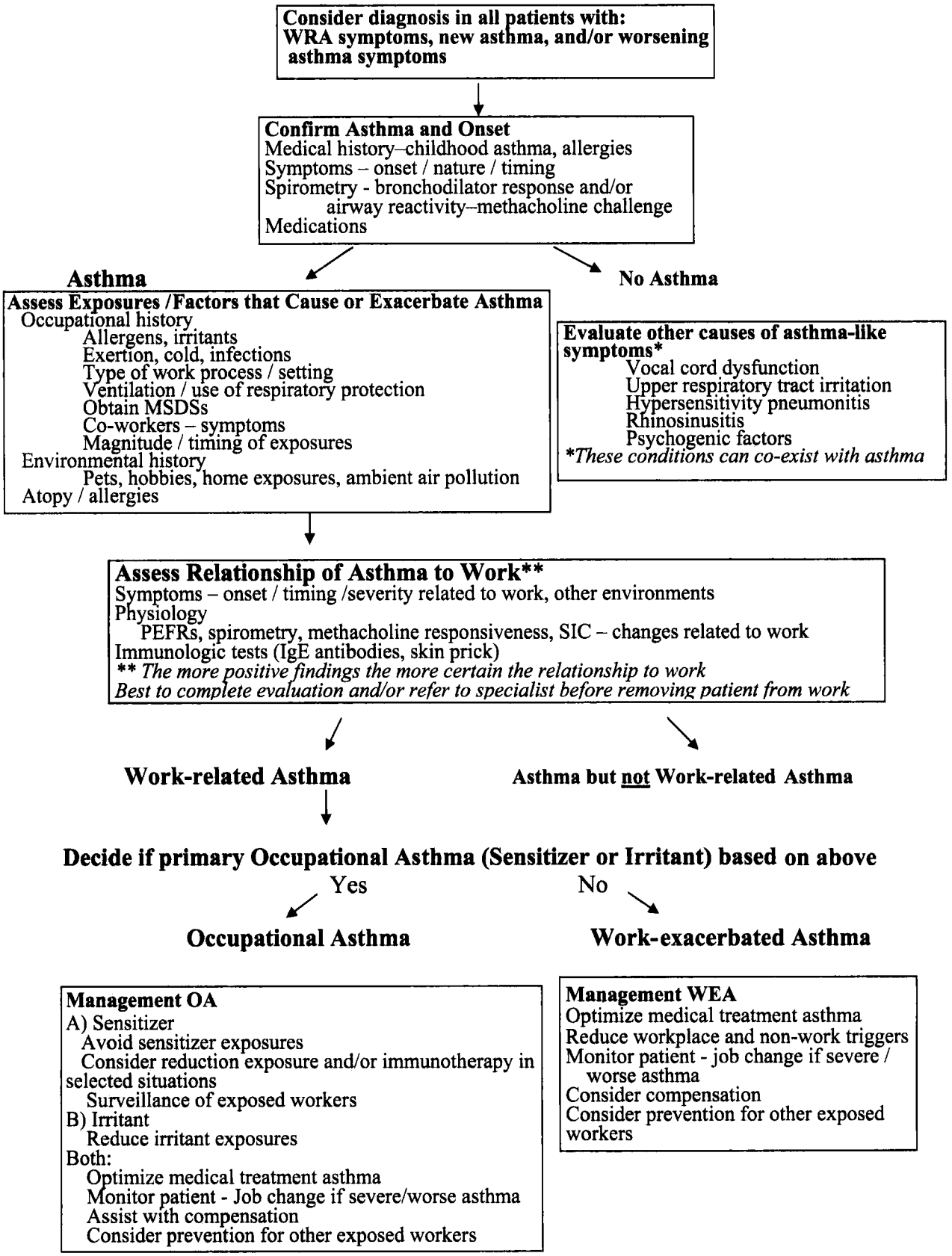

FIGURE 2. Summary flow chart of clinical evaluation and management of WRA.

work allergens when these tests are technically reliable and available.

8. **In individuals with suspected sensitizer-induced OA, conducting an SIC (where available) is suggested when the diagnosis or causative agent remains equivocal; however, this testing should only be performed in specialized facilities, with medical supervision throughout the testing.**
9. **For all individuals with WRA, attempt better control of exposures. Remove patients with sensitizer-induced OA from further exposure to the causative agent in addition to providing other asthma management.**
10. **In individuals with irritant-induced asthma or WEA, the panel advises optimizing asthma treatment and reducing the exposure to relevant workplace triggers. If not successful, change to a workplace with fewer triggers is suggested in order to control asthma.**
11. **For workers who are potentially exposed to sensitizers or uncontrolled levels of irritants, the panel advises primary prevention through the control of exposures (*eg*, elimination, substitution, process modification, respirator use, and engineering control).**
12. **An individual diagnosis of OA represents a potential sentinel health event:**
    - **Evaluate the workplace to identify and prevent other cases of OA in the same setting; and**
    - **For work environments with potential exposure to sensitizers, the Panel advises secondary preventive measures including medical surveillance using tools such as questionnaires, spirometry, and, where available, immunologic tests.**

Introduction

WRA, which includes OA and WEA, presents a major health challenge with significant potential for acute morbidity, long-term disability, and adverse social and economic impacts.[3] Since the 18th century, medical writers have noted links between certain trades and respiratory symptoms recognizable today as asthma. In the 20th century, the number of work-related causes of asthma (sensitizers) expanded substantially. By the mid-1980s, recognition grew[4] that acute irritant exposure could cause asthma in an etiologic process that is distinct from that of sensitizers. Currently, hundreds of distinct causes of OA have been recognized.[1,5–7] WEA has received less systematic study, yet has been recognized as a priority area for further research.[8,9]

The prevalence of WRA has not been well defined due in part to variable definitions, diagnostic criteria, and work settings, as well as limited surveillance data. It has become clear that WRA is a far more substantive component of adult asthma than has been appreciated from clinical case series, or from studies of individual worksites or single industries. Approximately 10 to 15% of cases of adult asthma are attributable to occupational factors, which is consistent with a role for work in initiating asthma.[10–13] The incidence of OA has been difficult to measure with precision. OA surveillance data vary widely in case capture, underestimating the true extent of the problem. As much as 25% of adult asthmatic patients are estimated to have WRA, which would include WEA as well as OA.[14] Consistent with this, in other studies[3,15–17] of patients in whom WRA has been diagnosed, the proportion of patients with WEA ranges from about 10 to 50% of cases of WRA, although this may be as reflective of compensation practices as of true prevalence.

The magnitude of WRA is matched by the important opportunities for the primary prevention of new cases and the secondary and tertiary prevention of disease progression and disability. Prevention is intimately linked both to the diagnosis and treatment of disease. The diagnosis of a single case of OA among a group sharing similar exposures offers the possibility of preventing new asthma (*ie*, primary prevention) or the progression of subclinical illness to frank disease (*ie*, secondary prevention) in other workers. Moreover, the appropriate management of WRA involves the control of the specific factors responsible for disease onset or exacerbation/aggravation, thus avoiding a situation in which ongoing exposure causes disease progression (*ie*, tertiary prevention).

Clinical practice in the diagnosis and management of WRA differs from standard asthma care in several important ways. In addition, critical aspects of this subject can be unfamiliar or daunting, even to practitioners who are well versed in standard clinical asthma care. The goal of this review is to provide guidance to health-care providers, including those who treat adult asthma patients in primary care practice, those approaching this question from a pulmonary or allergy care perspective, and clinicians working in occupational health settings.

To meet this ambitious goal, we include topics that have not typically been emphasized in standard practice guidelines, such as WEA and preventive

measures. A thorough occupational history is essential to the diagnosis of WRA, including the delineation of work-related exposures. General issues of evidence-based medicine and the diagnostic process have been well described.[18] Because of the limitations to diagnostic testing, the pretest probability of WRA based on symptoms and the occupational history (and the related Bayesian analysis of posttest likelihood) warrants particular consideration. Bayesian issues are especially relevant here because the diagnosis of occupational disease often demands a different level of diagnostic certainty than that used in other fields of practice. In occupational practice, the attribution of etiology is frequently benchmarked against a "more-likely-than-not" (*ie*, > 50% likelihood) standard (*eg*, for workers compensation and medicolegal determinations) rather than achieving a higher level of certainty, as is typically desired in standard clinical practice.

We will also address a combination approach based on the results of several diagnostic modalities used together, as opposed to a linear algorithm restricted to a stepwise series of tests. Although such an integrative approach is not typically emphasized in practice guidelines, it is especially relevant to the evaluation of WRA because testing choices are often limited by factors such as occupational status, access to the workplace, and logistical access to certain diagnostic modalities.

Despite limitations in the relevant literature and in the accuracy of the diagnostic modalities available, there is a tremendous need for guidance on how to diagnose and manage patients with WRA. It is important to remember that the goal of this Consensus Document is to assist clinicians along a management pathway, rather than to prescribe a specific checklist that must be fulfilled in order to achieve a valid clinical decision. Keeping these limitations in mind, we believe that this document based on published literature and supplemented with clinical expert guidance will assist clinicians to diagnose and treat WRA.

Materials and Methods

In 1995, the ACCP published ACCP Consensus Statement: Assessment of Asthma in the Workplace.[1] In 2005, the Health and Science Policy Committee of the ACCP chose to reexamine this topic. This new publication is intended to update and expand the previous review. The University of Alberta/Capital Health Evidence-Based Practice Center was commissioned to review the evidence in the areas of diagnosis and treatment of OA. An international panel of experts was convened to provide a document, synthesized from this evidence review and supplemented by an additional literature review, to inform pulmonary, occupational, allergy/immunology, and primary care practitioners on the diagnosis and management of WRA. Although initially intended to develop formal "evidence-based" guidelines, a Consensus Document has been developed as more fitting to the available published studies on WRA.

Panel Selection and Composition

Susan Tarlo, MBBS, FCCP, of the Department of Medicine at the University of Toronto (Toronto, ON, Canada) served as the Chair of this international panel of experts, representing a variety of specialties including pulmonary, occupational medicine, allergy, and clinical immunology. Many were members of ACCP; however, members of other organizations (*eg*, the American Thoracic Society; the Canadian Thoracic Society; the American Academy of Allergy, Asthma, & Immunology; the American College of Allergy, Asthma, & Immunology; and the Occupational and Environmental Medicine Association of Canada) were also invited to participate. The expert panel first met in August 2005 in Chicago, at which time they selected the final scope of the topics. Teleconference and e-mail communication supplemented that initial work.

Authors volunteered to draft sections of the document. The assignments were made by the steering committee based on known expertise and interest in the area; however, all committee participants reviewed the entire document, and contributed to discussion and consensus on the document and made suggestions. The proposals and suggestions in this document should not be used for performance measurement or for competency purposes, since they are not evidence based, as outlined by the ACCP Health and Science Policy Committee. This Consensus Document has been endorsed by the Canadian Thoracic Society and the Canadian Society of Allergy and Clinical Immunology.

Funding and Conflicts of Interest

Funding for the development of this document was supported by an educational grant from the Schering-Plough Corporation. No representatives from this company were granted the right of review nor were they allowed participation in any portion of the document development including participation on any conference calls or attendance at any meetings. The document authors were unaware of the origin of the funding and were not paid for their contributions.

The very stringent approach of the ACCP to the issue of potential or perceived conflicts of interest has created many firewalls to ensure that there are no influences from industry or other sources. This policy is available on the ACCP Web site (www.chestnet.org). All conflicts of interest within the preceding 5 years were required to be disclosed by

all panelists, at all face-to-face meetings, the final conference, and prior to submission of the Consensus Document for publication. The most recent of these are documented in this published Consensus Document. Furthermore, the panel was instructed in this matter, verbally and in writing, prior to the deliberations of the final conference. Any disclosed memberships on speaker's bureaus; consultant fees, grants, and other research monies; and any fiduciary responsibilities to industry were provided to the full panel in writing at the beginning of the conference and at the time of submission of the Consensus Document for publication.

Scope of the Consensus

For the purposes of this document, we consider WRA to include asthma initiated by workplace exposures (*ie*, OA) as well as preexisting asthma made worse by work exposures (*ie*, WEA). Other respiratory conditions, such as industrial bronchitis, work-related chronic obstructive disease and emphysema, or "asthma-like" syndromes associated with certain occupational exposures, will not be subsumed within this document, even though they may share characteristics with WRA. Most of the published literature has addressed OA rather than WEA. Nonetheless, the panel determined that it should be included in the present document since WEA is considered to be a type of WRA, can be difficult to distinguish from OA, and does have an important impact on morbidity, work time loss, and job efficiency.

Evidence Review

The evidence review for this clinical practice guideline included a systematic review commissioned by ACCP through the AHRQ on the diagnosis and treatment of OA, as well as topic specific searches following the completion of the systematic review.[11] In addition, the authors of specific sections of this document were encouraged to conduct searches and to supplement the evidence from knowledge of their topic area.

Formal systematic reviews performed by The University of Alberta/Capital Health Evidence-based Practice Center were focused on the diagnosis and management of OA. The diagnosis review focused on evidence from studies that reported an acceptable reference standard (usually an SIC[19] or clinical consensus) compared to a single diagnostic test or some combination thereof. The management review focused on evidence from studies that included patients in whom OA had been diagnosed, and for whom clinical outcomes had been reported at follow-up. A detailed description of the methods used can be found at www.ahrq.gov. For the ACCP document, additional and updated information was obtained regarding the domains of clinical history, and primary and secondary prevention.

The Consensus Panel also derived supplemental data from peer-reviewed publications up to 2007 (identified through searches of standard databases, including the National Library of Medicine PubMed database). When available data were limited, inconclusive, or conflicting, the panel relied on a consensus-reaching process in order to develop its final suggestions.

Limitations of the Evidence

High-quality evidence is particularly problem ridden in WRA. First, for diagnostic tests there is no "gold standard" against which to determine sensitivity and specificity. Although SIC served as a "reference standard" for OA in the initial evidence-based literature review that we utilized,[11] our Consensus Document is circumspect in comparing SIC testing to other diagnostic approaches for several reasons. OA is not a single disease, and diagnostic tests evaluated in one clinical setting, such as bakers' asthma, may not be applicable to other conditions, such as diisocyanate-induced asthma or irritant-induced OA. Additionally, several diagnostic approaches depend on the worker still being at the job in question, as well as the ability to remove the worker from work exposures for days to weeks during testing followed by a return to work, which is difficult to achieve in many real-world situations. Second, for treatment and management issues in patients with WRA, there have been few controlled clinical trials (as noted previously), and such trials are unlikely to be performed in the future. Thus, ecologic data, temporal trends, and case reports (which were excluded from the original evidence-based review) must be relied on to supplement traditional RCT evidence. Indeed, several of the suggestions ultimately reached in the Consensus Document are based on the strength and consistency of observational studies.

Methods of Consensus, Document Writing, and Validation

Throughout the process of development of the Consensus Document, expert consensus was reached whereby all panel members came to agreement, as follows: by panel discussions, including e-mail communications, conference calls, and two face-to-face meetings, which allowed any differing views to be expressed and modifications of wording to be made

in order to achieve consensus. The writing groups and the executive committee of the panel extensively reviewed each section during the writing process, and the entire panel received each full draft for comments and discussion. A final conference provided an opportunity for the entire panel to review and discuss the document. Following final revisions and one final review by the executive committee and the full panel, the Consensus Document was reviewed and approved by the ACCP Health and Science Policy Committee, the ACCP Occupational Disease Network, and the ACCP Board of Regents. These reviews were performed prior to endorsement by the Canadian Thoracic Society and the Canadian Society of Allergy and Clinical Immunology. The document has not been field tested. Institutional research ethics board approval was not sought for this project, which consisted of the review of published data and achievement of expert consensus.

Disclaimer

The extracts of NRL mentioned in the Consensus Document that have been used for skin testing and treatment for allergy to NRL have not been approved in the United States for the purposes under discussion. In addition, for many of the occupational sensitizers discussed in the Consensus Document, there are no commercial and approved extracts in the United States for skin testing and/or treatment, many of which have only been used in research studies. There are commercially available mammalian epidermal extracts (*eg*, cat) that have been approved in the United States for the treatment of allergy confirmed by demonstration of specific IgE, but have not been specifically approved for indications of occupational allergy or occupational asthma. Food allergens are not approved in the United States for immunotherapy. Omalizumab is currently approved in the United States for patients with asthma who fulfill certain criteria but is not currently approved in the United States for the treatment of specific occupational allergy or occupational asthma. The other medications that are discussed in this Consensus Document have been approved in the United States for general asthma treatment.

Definitions

The ACCP committee that composed this document has arrived at the following consensus definitions for WEA and OA. *WRA* is the broad term that refers to asthma that is exacerbated or induced by inhalation exposures in the workplace.[20] The term *WEA*[1,21–23] refers to asthma triggered by various work-related factors (*eg*, aeroallergens, irritants, or exercise) in workers who are known to have preexisting or concurrent asthma (*ie*, asthma that is occurring at the same time but is not caused by workplace exposures). Some differentiate between WEA and work-aggravated asthma, based on whether the worker returns to a prior asthma baseline (WEA) or not (work-aggravated asthma); but, this distinction is not widely accepted, and this Consensus Document will use the term *WEA*.

The term *OA* refers to *de novo* asthma or the recurrence of previously quiescent asthma (*ie*, asthma as a child or in the distant past that has been in remission) induced by either sensitization to a specific substance (*eg*, an inhaled protein [high-molecular-weight (HMW) protein of > 10 kd] or a chemical at work [low-molecular-weight (LMW) agent]), which is termed *sensitizer-induced OA*, or by exposure to an inhaled irritant at work, which is termed *irritant-induced OA*[1] (Fig 1). OA due to a sensitizer presents with a latency period and includes those causative agents (proteins and some chemicals) for which sensitization can be demonstrated (typically by antigen-specific IgE) in most persons with asthma due to exposure to that agent. It also incorporates OA caused by those agents (usually reactive chemicals) for which an immunologic mechanism is strongly suspected, yet an antigen-specific immune response cannot easily be tested in most affected workers. This definition of OA is consistent with other definitions. It also encompasses irritant-induced asthma (with no apparent latency period).[24–28] The most definitive form of irritant-induced asthma is reactive airways dysfunction syndrome (RADS), which describes an acute onset of asthma after a single, very high irritant exposure.[4] Earlier definitions of OA typically referred only to sensitizer-induced asthma and not to irritant-induced asthma.

These definitions are interpreted with the understanding that WEA and OA are not mutually exclusive and may coexist in the same worker.[1] In contrast to WEA, the onset of asthma due to work exposures in a person with a history of asthma as a child or in the distant past is considered more likely to be new-onset OA, not WEA, although the recurrent onset of asthma unrelated to work and subsequent WEA is also possible.

In summary, WRA encompasses both OA and WEA, which may coexist in individual workers (Fig 1). OA includes asthma caused by exposure to sensitizing agents and/or irritants in the workplace. A history of childhood asthma does not exclude the possibility that OA may develop after an appropriate workplace exposure. Studies on WEA and irritant-induced OA are limited compared to those on sensitizer-induced OA, leading to relative uncer-

tainty regarding the definition, prevalence, diagnosis, and management of WEA and irritant-induced asthma.

General Asthma Considerations

Before considering specific aspects of WRA, it is helpful to review some features of general asthma, since the majority of patients with WRA will initially present to their physician with asthmatic symptoms. Furthermore, the diagnosis of WRA requires, first, that asthma be diagnosed; and, second, that the relationship with work be established. The possibility of WRA should be considered in all adult patients who are currently employed, and in those in whom asthma started or worsened during their working life.

The Global Initiative for Asthma[29,30] describes asthma as a heterogeneous chronic inflammatory disorder of the airways associated with airway hyperresponsiveness and recurrent episodes of wheezing, dyspnea, chest tightness, or cough. Episodes are usually associated with variable airflow limitation that is often reversible, either spontaneously or with treatment. It must be appreciated, however, that these features are not specific for asthma (other respiratory disorders share some or all of them), and that there can be significant variability and heterogeneity in the clinical presentation of asthma. There are also several conditions that coexist with, exacerbate, or mimic asthma such as rhinosinusitis,[31] gastroesophageal reflux disease,[32,33] laryngopharyngeal reflux,[34] paradoxical vocal fold motion disorder (also known as *vocal cord dysfunction* [VCD]),[35,36] or chronic subacute infections by Mycoplasma or Chlamydia.[37] The clinical evaluation of asthma patients requires a comprehensive history, a thorough physical examination, and pulmonary function testing. The history should detail any precipitating events, whether onset was in childhood or as an adult, and whether there is a personal history of allergies or a family history of asthma and allergies. The characterization of symptoms (*eg*, shortness of breath, chest tightness, cough, and/or wheezing); triggers in the home and work environment; and worsening by season, exercise, or night support the diagnosis and aid in the management of asthma.

A physical examination helps to assess the severity of airflow obstruction as well as signs of extrapulmonary disease (*eg*, nasal congestion or cardiac disease that may contribute to, or mimic, asthma symptoms). The principal physical finding in asthma is expiratory wheezing, but the absence of wheezing does not rule out asthma.

The assessment of asthma by history and physical examination may be misleading; thus, it is important to carry out pulmonary function testing. Measurements of airflow obstruction, its reversibility, and its variability are important in establishing the diagnosis of asthma.[29] Spirometry and peak expiratory flow recordings (PEFRs) directly assess airflow obstruction. Reversible airflow obstruction is a key feature of asthma, but many asthmatic patients may have normal or near-normal pulmonary function, especially during nonexacerbation periods or due to treatment. In the case of OA, test results may be normal if the patient has not recently been exposed to the relevant work agent or is receiving asthma medications. While the accepted response to bronchodilator therapy in asthma patients is a $> 12\%$ and a > 200-mL improvement in FEV_1,[38] their absence does not rule out asthma.[39] The measurement of variability in airflow limitation using a peak expiratory flowmeter over a 2-week period can also help to support a diagnosis of asthma. A diurnal variation in PEFRs of $\geq 20\%$ is considered to be a diagnostic criterion.[40] In patients with symptoms consistent with asthma but normal lung function, the measurement of airway responsiveness to methacholine, histamine, or exercise challenge may help to establish the diagnosis of asthma. In the context of sensitizer-induced OA, such tests are preferably performed soon after a work exposure (*ie*, within 24 h after a typical exposure). Such challenge tests are sensitive for the diagnosis of asthma, but are not specific since airway hyperresponsiveness can be found with other conditions (*eg*, allergic rhinitis or bronchiectasis)[41] or in the absence of any clinical condition. The absence of airway hyperresponsiveness on challenge testing has a fairly high negative predictive value (NPV) for current symptomatic asthma, and generally can be used to rule out active disease.[42] As we will detail in a later section, however, there have been documented reports, although uncommon, of persons without nonspecific hyperresponsiveness who do respond to SIC with the workplace agent to which they have been sensitized. Ancillary laboratory studies such as skin-prick tests (SPTs), radioallergosorbent tests (RASTs), and measurements of total IgE levels provide evidence for an allergic response to environmental, workplace, and/or food allergens. The health-care provider should make the diagnosis of asthma with the combination of consistent symptoms and pulmonary function test findings because the consequences for the patient are considerable.

Differential Diagnostic Considerations

There are several reported conditions that manifest clinical presentations that can be mistaken for WRA or may coexist with WRA. These will be briefly reviewed before discussing methods of diagnosis of WRA. These alternative diagnostic possibilities can be differentiated from WRA through obtaining a careful history and conducting appropriate labora-

tory testing, and are important to identify since their management differs from that of WRA.

Asthma-Like Symptoms and Odor Triggers: A spectrum of clinical responses besides asthma may occur after irritant exposures. Irritant exposures can lead to an enhanced cough reflex,[43,44] poorly defined illnesses, such as an increased awareness of irritants,[45] and asthma-like symptoms with cognitive complaints similar to multiple chemical sensitivity/idiopathic environmental intolerance.[46,47] A number of asthmatic patients have noted an enhanced response to odorants and irritants.[48,49] Nonetheless, sensitivity to chemicals in the environment,[46,47] which is defined as becoming ill after smelling chemical odors like perfume, has been reported in 15 to 30% of the general population.[47] The term *sensory hyperreactivity* has been used to describe patients who complain of upper airway symptoms induced by scents and chemicals[50] and show increase cough sensitivity by capsaicin challenge, but no increased responsiveness to methacholine.[44,50]

VCD: One of the most common clinical syndromes that mimics asthma is VCD, which is also included in the term *irritable larynx syndrome* or *episodic paroxysmal laryngospasm.*[51] Vocal cord closure usually occurs on inspiration, causing airflow obstruction, wheezing, and occasionally stridor. About 10% of patients referred for refractory asthma experience VCD; an additional 33% of patients have VCD accompanying asthma. A temporal association between VCD onset and irritant exposure has been described.[52] The mechanisms of VCD remain unknown, although underlying gastroesophageal reflux and psychogenic factors may contribute. Irritants, chemicals, certain odors, exercise, and methacholine challenge may precipitate attacks in VCD patients. A definitive VCD diagnosis requires visualization of the vocal cords via laryngoscopy, showing adduction of the anterior two thirds of the vocal cords during inspiration that may persist into expiration. Speech therapy and treatment of any underlying gastroesophageal reflux are the first lines of treatment for VCD.

Eosinophilic Bronchitis: Eosinophilic bronchitis is a term describing subjects with large numbers of eosinophils found on sputum examination and without evidence of asthma. A nonproductive cough, the absence of airway obstruction, and hyperresponsiveness characterize the clinical presentation, which has been reported in workers exposed to acrylates,[53] latex,[54] mushroom spores,[55] and lysozyme.[56]

Diagnosis of WRA

The History in WRA

In every adult whose asthma begins or worsens while working, the possibility of WRA should be considered and evaluated. There is consistency in the published literature indicating that patients with WRA have a history supportive of the diagnosis, and this has been used as the basis for further investigations. Thus, a necessary first step in evaluating patients with asthma of working age is to obtain a detailed and accurate history. In addition to providing information about asthma symptoms, the history should identify any temporal relationships between asthma symptoms and work, and should detail information about work status and exposure characteristics. Although transient work-related aggravation/exacerbation of asthma is often diagnosed in asthmatic patients based on history alone (including history of exposure and reported medication needs), the history findings are generally not sufficient alone to diagnose other WRA. Thus, added objective tests should be performed, especially for detection of sensitizer-induced OA.

Respiratory symptoms present in WRA patients (*ie*, cough, wheeze, shortness of breath, and chest tightness) are identical to those present in non-OA patients. They may be accompanied by or preceded by symptoms of rhinitis and/or conjunctivitis. Specific inquiry should be made to determine any relationship between the workplace and symptoms. This is especially pertinent for sensitizer-induced OA and for WEA where an improvement in symptoms typically occurs during times away from work (*eg*, on weekends and during vacations) and worsens on days with regular or intermittent exposures at work. The following key questions should be asked of any patient with asthma starting or worsening during their working life:

- Were there changes in work processes in the period preceding the onset of symptoms?
- Was there an unusual work exposure within 24 h before the onset of initial asthma symptoms?
- Do asthma symptoms differ during times away from work such as weekends or holidays or other extended times away from work?
- Are there symptoms of allergic rhinitis and/or conjunctivitis symptoms that are worse with work?

Changes in work processes may entail exposure to a new agent to which the worker has not been previously exposed or to increased levels of exposure to an agent that was previously present. Sensitizing agents carry an increased risk of sensitization and OA, especially in the first few years of exposure, although this can occur after many years of ongoing contact. WEA could occur from a change in work area or process with increased exposure to conditions

triggering asthma, but could also occur without a specific change at work if the underlying asthma worsens or is less well controlled than usual (*ie*, there is an increasing susceptibility to previously tolerated work conditions). As an example, a worker with asthma may have an exacerbation from cold air or sulfur dioxide exposure at work only when the worker has a concurrent respiratory viral infection and an associated worsening of underlying airway hyperresponsiveness.

An unusual exposure at work (*eg*, a spill or other high-level exposure) to a potentially irritant chemical or chemicals, especially within 24 h before the onset of the first asthma symptoms, raises the suspicion of irritant-induced asthma. Typically, symptoms are severe enough to require first aid or emergency treatment at that time. RADS is the most definitive form of irritant-induced asthma. The original diagnostic criteria for RADS (Table 1)[4] include a single, massive exposure to an irritant gas, vapor, or fume with an immediate onset of asthma symptoms or within 24 h of the exposure. Cases that do not meet these stringent criteria (*eg*, where there is a lag of several days before the onset of symptoms, or when there is no single massive exposure but rather repeated exposures over days or weeks,[25] less massive exposures, or a shorter duration of symptoms) are subsumed under a broader category of "irritant-induced asthma."[57,58]

Improvement in asthma symptoms while off from work or on holiday is not specific to WRA (patients with other asthma can also feel better when not at work), but this is a sensitive indicator for OA related to a work sensitizer (especially relatively early in the course of disease) and for WEA. A positive response occurs in about 88 to 90%[59–61] of those patients with confirmed sensitizer-induced OA vs 76% of those without OA (but who still may have had WEA).[59] Of those patients with asthma that was not work related, 41% and 54%, respectively, have reported[60] improvement during weekends and holidays, emphasizing the need for additional, objective tests for accurate diagnosis. Airway responses to LMW (chemical) sensitizers are more commonly isolated late responses, and workers can present with evening cough or other asthma symptoms after work as the primary symptom(s), with improvement at times requiring several days away from exposure.

Additional work-related symptoms of allergic rhinitis increase the probability of sensitizer-induced OA, while work-related dysphonia (which is more consistent with VCD) has been negatively associated with OA.[61] When compared with a SIC carried out in a compensation referral case series,[61] false-positive diagnoses often occurred, both for OA and for asthma itself, when using history findings alone (34% of those with a positive history of asthma had no asthma based on objective test results). In that population, the presence of wheezing that was worse at work and nasal itching at work showed the greatest historical value for challenge-proven OA (positive predictive value [PPV], 0.89 and 0.53, respectively; NPV, 0.32 and 0.70, respectively; sensitivity, 0.40 and 0.48, respectively; specificity, 0.85 and 0.74, respectively). As would be expected, nasal itching was a more sensitive factor among those exposed to HMW sensitizers. Loss of voice at work carried a significant negative value. However, a model developed from this study was correctly predictive in only 42% of subjects, emphasizing the need for further investigations when the diagnosis is suspected. As with other clinical studies that include SIC, the population was confined to those in whom WRA was already suspected, and the predictive values and sensitivity/specificity have not been assessed as yet in a population of unselected asthmatic patients.

Table 1—*Diagnostic Criteria for RADS, the Best-Defined Form of Irritant-Induced Asthma

1. There is an absence of preexisting respiratory disorder, asthma symptomatology, or a history of asthma in remission and an exclusion of conditions that can simulate asthma
2. The onset of asthma occurs after a single exposure or accident
3. The exposure is to an irritant vapor, gas, fumes, or smoke in very high concentrations
4. The onset of asthma symptoms develops within minutes to hours and < 24 h after the exposure
5. There is a positive methacholine challenge test finding or equivalent test, which signifies hyperreactive airways, following the exposure
6. There may or may not be airflow obstruction confirmed with pulmonary function testing
7. There is exclusion of another pulmonary disorder that explains the symptoms and findings

*Adapted from Brooks et al.[4]

Exposures and Exposure Assessment

Although not subjected to evidence-based studies, a detailed work exposure history, enabling the determination of likely exposure to a known workplace sensitizer or irritant, can affect the pretest probability of WRA. The exposure history should focus particularly on exposures occurring at the time that asthma started or worsened at work. There are > 250 reported workplace sensitizers and multiple at-risk workplace settings. Many of these (based on reports in the published literature up to 2002) are listed on a Web site at www.asmanet.com (following links to OA, user guide); however, the absence of exposure to a previously identified sensitizer does not exclude OA. Examples of common jobs and specific agents are shown in Tables 2,[62] 3, and 4;

agents are typically classified according to whether they are of HMW (usually protein) or LMW (small chemical). Multiple exposures can occur in the same work area, termed *mixed environments*, with both sensitizers and irritant exposures, which can interact to increase the risk of asthma. Common occupations reported in a North American report[63] of WRA include teachers, farm workers, and construction workers.

Exposure levels of a work sensitizer can be difficult to quantify, especially when exposures are variable and intermittent. The risk of sensitization is typically greater with higher and more frequent exposures, as has been shown for certain agents for which more extensive industrial hygiene data are available.[64] Respiratory protective devices may be used to reduce exposure to sensitizers but do not provide complete protection. Sensitization and/or the precipitation of symptoms may still occur despite respirator use or in settings where measured air levels are extremely low or nondetectable. Skin exposure may be an important route of sensitization with some agents such as diisocyanates.[65,66]

Commonly reported causes of irritant-induced OA include accidental spills or other high-level exposures to acids, chlorine or chlorine compounds, alkaline dusts, smoke (through inhalation), and aldehydes (Table 5). Diverse occupational exposures, populations, and host factors have been associated with an increased risk of WEA (Table 5). There have been differences between studies in asthmatic and comparison populations, those with disparate clinical and exposure data available, and those using variable diagnostic criteria, all of which are factors that can also hamper the comparison of studies.[8,15,60,67–70] Several studies[8,68,71] have suggested a healthy worker effect, where asthmatic patients avoid or leave workplaces with higher exposures to asthma triggers such as irritants, allergens, or extreme temperatures. Together, the findings of the available studies suggest that irritants are the most frequently reported workplace exposures for those with a history of WEA.[15,60,69,70] Frequently, the reported exposures include mineral and inorganic dusts, chemicals, paints, temperature extremes, cleaning agents, second-hand cigarette smoke, and poor indoor air quality.[15,60,67,69,70] Work exposure to common asthma triggers such as cold air, physical exertion, viral infections, and plant, mold, and animal allergens can also exacerbate

Table 2—*Work Factors to Consider for Possible Risk of OA and Illustrative Examples*

OA	Examples
Sensitizer-induced OA	
Agent	Examples given in Table 4
Industry	Health care (latex, formaldehyde, and glutaraldehyde); autobody shop (diisocyanates)
Job title	Hairdresser (persulfates);
Task performed	Cleaning; industrial liquid transfers
Mixed environments	Metalworking; agriculture; textile production
Mitigating factors	Respirators; exhaust ventilation system
Irritant-induced OA (without latency [*eg*, RADS])	
Incidents	Specific reported incident with high levels of exposure
Agent	Chlorine gas
Occupation	Firefighter, actor (irritant smokers), cleaner
Industry	Pulp mill, chemical production

Table 3—*Examples of Occupations/Industries With Sentinel Health Events for Sensitizer-Induced OA*

Industry, Process, or Occupation	Selected Agents
Jewelry, alloy and catalyst makers	Platinum
Polyurethane, foam coatings, adhesives production, and end-use settings (*eg*, spray painters, and foam and foundry workers)	Isocyanates
Alloy, catalyst, refinery workers	Chromium, cobalt
Solderers	Soldering flux (colophony)
Plastics industry, dye, insecticide makers, organic chemical manufacture	Phthalic anhydride, trimetallic anhydride (used in epoxy resins)
Foam workers, latex makers, biologists, and hospital and laboratory workers	Formaldehyde
Printing industry	Gum arabic, reactive dyes, and acrylates
Metal plating	Nickel sulfate and chromium
Bakers	Flour, amylase, and other enzymes
Woodworkers and furniture makers	Red cedar (plicatic acid) and other wood dusts
Laboratory workers and animal researchers	Animal proteins
Detergent formulators	Detergent enzymes such as protease, amylase, and lipase
Seafood (crab, snow crab, and prawn) workers	Crab, prawn, and other shellfish proteins
Health-care workers and nurses	Psyllium, NRL, glutaraldehyde, methacrylates, antibiotics, and detergent enzymes
Laxative manufacture and packing	Psyllium
Hairdressers and manicurists	Persulfates and acrylates (artificial nails)

*Adapted from Mullan and Murthy.[62]

Table 4—*Illustrative Examples of Specific Agents (and Workers) Associated With Sensitizer-Induced OA*

HMW Agents	Selected Examples	LMW Agents	Selected Examples
Plant antigens	Cereals, flour; green coffee bean; tobacco; gums	Isocyanates	Polyurethane foam production and end-user applications (auto spray painters)
Animal antigens	Rodents; cats and dogs; farm animals; mites	Wood dusts	Western red cedar (carpenters and sawmill workers)
Bioaerosols	Molds and bacteria	Highly reactive compounds	Anhydrides, amines, and acrylates
Enzymes	Detergent enzymes, amylase in baking	Aldehydes	Glutaraldehyde and formaldehyde
Latex	Gloves (health-care workers and others)	Colophony	Solder fluxes
Seafood	Crab, prawn, and fish	Dyes	Reactive dyes (textile workers)
Drugs	Antibiotics; Psyllium laxatives	Persulfate	Hairdressers
		Metals	Metal plating (chromates, nickel, and cobalt), platinum (catalysts)

asthma at work. WEA or WRA has been reported in a wide range of occupations and work settings, including cleaners, teachers, production, and service and construction workers.[63,72,73]

The job title may not accurately identify a worker's exposure, since there also may have been exposures from activities carried out by nearby workers. Therefore, it is important to ascertain exposures not only from the job in question, from but also those of others in the same work environment. Patients may not know what agents are used at work. Despite limitations, useful information can be obtained by asking the patient to obtain copies of MSDSs from the workplace. The US Occupational Safety and Health Administration (OSHA) requires suppliers to include an MSDS with each shipment of an industrial material or chemical, and workers are entitled to receive copies of these sheets. OSHA requires that sensitizers with a $\geq$ 1% presence in a chemical product ($\geq$ 0.1% in Canada) be listed as hazardous ingredients. A note given to the patient can help to obtain MSDSs for products used by the patient or coworkers. MSDSs generically identify hazardous ingredients, provide cursory but important toxicologic information, and recommend safety and emergency procedures. OSHA requires the employer to maintain MSDSs onsite and to make them available to physicians and workers. A physician has the right to contact the employer or the supplier by telephone or written request for MSDS information. It is also possible to acquire MSDS information through the internet. Identification of the agent allows access to further in-depth information via standard textbooks and publications. If sensitizer OA is suspected, it may be necessary to request additional information from the product manufacturer or the workplace (always with the patient's permission).

Sources of information about work exposures and MSDSs are given in Table 6. Knowledge of the major exposures seen in certain jobs or industries can also help to identify potential causative agents, as are shown in Tables 3 and 4, which are not intended to list all

Table 5—*Common Agents in Irritant-Induced OA and WEA*

Asthma	Common Agents
Irritant-induced OA (high-level respiratory irritant exposures)	Spills of chlorine, glutaraldehyde
	Smoke (from fires)
	High-level irritant dust (*eg*, from the World Trade Center collapse)
	Spills of volatile diisocyanates
	Accidental mixtures or reactions of chemicals (*eg*, bleach and ammonia)
	Accidental high-level chlorine exposure as in paper mills
WEA (moderate-to-low-level exposures with underlying asthma)	Exposures to dusts, smoke, fumes, and sprays (*eg*, industrial sources, second-hand smoke, and cleaning products in buildings)
	Physical factors (*eg*, temperature or humidity extremes, and exertion)
	Viral or other respiratory infections related to work that exacerbate asthma (*eg*, in health-care workers or teachers)
	Common allergen exposures at work (*eg*, teachers exposed to pets or fungal spores in classrooms, cleaners exposed to dust mites/animals, and office workers exposed to fungal spores)
	Mixed exposures of allergens and irritants (*eg*, cleaners exposed to dust mites/animals/fungal spores and also cleaning products)

Table 6—*Sources of Information About Exposure*

Sources of Information	Examples of Web Sites
Worker descriptions	
General sources	http://www.asmanet.com www.asthme.csst.qc.ca (in French) http://hazmap.nlm.nih.gov/ http://toxnet.nlm.nih.gov/
MSDSs*	http://ccinfoweb.ccohs.ca/msds/search.html www.med.cornell.edu/ehs/msds.htm
Textbooks and published medical literature	Appendix in *Asthma in the Workplace*[5]
Unions	
Government agencies	NIOSH: http://www.cdc.gov/niosh, (RTECHS); Agency for Toxic Substances & Disease Registry: www.atsdr.cdc.gov; http://toxnet.nlm.nih.gov
Employer	
Occupational health consultant visit to plant	
Industrial hygienist; occupational physician	

*MSDSs may suffer from the omission of sensitizing agents or may fail to mention the toxicologic properties of ingredients that are included such as sensitization, asthma, or wheeze.

possible agents or occupations. Further exposure information is available from several publications.[74–76]

Additional Features in the History

Patients with OA from exposure to HMW sensitizers (and those with WEA due to a common aeroallergen in the workplace) [examples given in Table 5] commonly have associated symptoms of allergic rhinitis and conjunctivitis when exposed.[77] These symptoms may start prior to the onset of OA or may start concurrently.[78]

The onset of asthma symptoms related to a sensitizer occurs after a latent period of exposure, which can range from weeks to years, in contrast to the onset of RADS, which typically begins within 24 h after a very high irritant exposure. The latency period for LMW sensitizers (*eg*, diisocyanates and plicatic acid) and for some HMW sensitizers (*eg*, laboratory animals) is typically within 2 years of ongoing exposure,[7,79,80] while it is typically slightly longer for other HMW sensitizers such as flour or latex,[7,81] although there is a wide range for both (up to ≥ 20 years after starting exposure). Once sensitizer-induced OA is present, the timing of worsened asthma symptoms in relation to work exposures can range from immediate (*ie*, within minutes of further exposure to the sensitizer), to late (*ie*, typically 4 to 8 h after exposure, and more common as an isolated late response when the sensitizer is an LMW agent), or as a dual response (*ie*, an immediate response followed by a late response, as illustrated in Fig 3). The association with work may be less obvious if an isolated late response occurs, such as asthma symptoms in the evening after work. Improvement away from work may not be evident for several days or longer away from exposure and therefore may be noted only during a holiday period.

Although the improvement of symptoms away from work is a sensitive marker of sensitizer-induced OA, it is not perfect. In a subgroup of workers with sensitizer-induced OA, asthma does not improve or may even worsen, despite removal from work.[11] Lack of improvement has occurred more commonly when there has been a longer period of time of exposure and more severe asthma at the time of diagnosis, emphasizing the need for early diagnosis. Therefore, in a patient with long-standing asthma who is still working with exposures similar to those at the onset of asthma, a lack of a current work relationship from history would be less likely to exclude the diagnosis of sensitizer-induced OA.

Atopic workers are in general more likely to have asthma than are nonatopic workers, and they are also more likely to experience WRA symptoms.[10] The clinical features of those patients with WEA, such as severity or duration of symptoms, atopy, or medication use, are not consistently different from the clinical features of those patients classified with asthma not related to work or of those with OA.[8,15,60,69,70] Thus, this does not reliably distinguish among these forms of asthma. Although the diagnosis of WEA is frequently made on the basis of history and exposure features, the possibility of OA in such patients also requires consideration and, when appropriate, additional diagnostic tests.

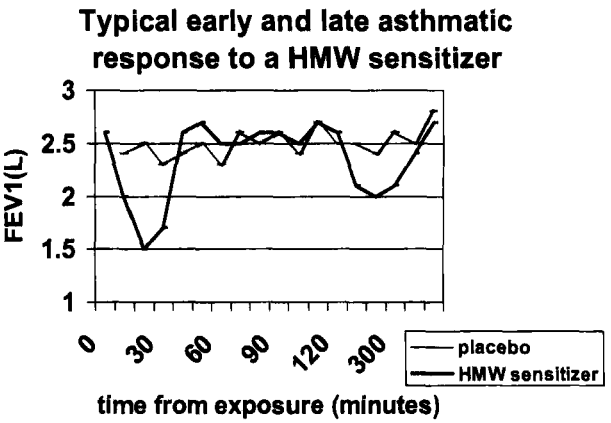

FIGURE 3. Typical dual asthamatic response including an early and a late component as measured by FEV_1 after exposure to an HMW sensitizer in a patient with OA.

Influence of Pretest Probability From History on Posttest Probability of OA

Although the probability of OA from history cannot be accurately quantified, a typical history and consistent exposure could lead to a high pretest probability (*eg*, ≥ 70%) before additional investigations are performed. This pretest probability influences the posttest probability of OA after the performance of subsequent investigations such as methacholine challenge and/or the assessment of the relationship of specific IgE to a work allergen, when feasible (Fig 4[82]). Conversely, a paucity of suggestive factors from history (*eg*, pretest probability of OA of around 15%) will result in a low posttest probability of OA, even when the results of other investigations are positive (Fig 4).

The incorrect diagnosis in 26% of suspected cases of sensitizer-induced OA from history alone compared with SIC[61] (in a compensation referral series), emphasizes the importance of the further assessment of those with a positive history of OA[74,83] in order to avoid unnecessary job change. Although further diagnostic testing should always be attempted, the correct diagnosis in almost 75% of patients based on history alone also demonstrates the importance of a careful history and that occasionally the history (among those with asthma) may be sufficient to diagnose OA, especially in cases of irritant-induced OA. Thus, the history has high sensitivity, and without an appropriate medical history the patient is unlikely to undergo the objective tests needed to make the correct diagnosis.[74,83]

Panel Consensus

1. In all individuals with new-onset or worsening asthma, take a history to screen for WRA (OA and WEA). Then confirm the diagnosis of asthma and investigate to determine whether the patient has WRA, whenever possible performing these tests prior to advising the patient to change jobs.
2. In all individuals with suspected WRA, obtain a history of job duties, exposures, industry, use of protective devices/equipment, the presence of respiratory disease in coworkers, and consult MSDSs, which list many recognized hazardous agents. Document the onset and timing of symptoms, medication use, and lung function, and their temporal relationship to periods at and away from work.
3. In individuals who have asthma not caused by work but that subsequently worsens while working, consider the diagnosis of WEA, which is usually based on changes in symptoms, medication use, and/or lung function temporally related to work.

Using a Combination Approach for Diagnosis

The tests described in the sections below supplement the initial medical and occupational history, physical examination, and pulmonary function tests.[74,83,84] Objective testing is not pursued consistently in all cases of suspected sensitizer-induced OA, in part due to practical limitations, such as the availability of testing. A combination of objective measurements has been advised in previous Consensus Statements,[1,74] and an aggregate of consistent objective findings, in addition to the asthma diagnosis and history, improves the diagnostic accuracy for sensitizer-induced OA.

Patients who have confirmed asthma, a temporal relationship of symptoms with workplace exposures, and appropriate work exposures typically have a high pretest probability for sensitizer-induced OA. Probability increases further with each additional positive diagnostic test result that supports a work relationship, and decreases with negative test results. The benefit derived from multiple tests to confirm or rule out sensitizer-induced OA depends to some degree on the pretest probability of the diagnosis. However, the use of multiple tests even in those with a high pretest probability can be useful. For example, if the test results are negative, they may suggest that sensitizer-induced OA is unlikely and may prevent a job change.[11]

Although used as a reference standard for comparison with other diagnostic tests, SICs are not widely available in North America (outside Quebec), may have false-positive or false-negative results, and have generally been considered only if other test results have been inconclusive or if other tests cannot be performed. Analyses of the added value of combination testing over single tests are very limited. The AHRQ review[11] showed that when a single test of airway responsiveness was compared to the combination of airway responsiveness and a test for sensitization (either SPT or serology), there was an added benefit. The published studies included in the estimates involved HMW antigens and, when pooled, revealed an estimated sensitivity of 83% and a specificity of 100% (compared with the reference standard of SIC that was used by the AHRQ review) when the results of a single test for nonspecific airway responsiveness and a skin test to a workplace HMW agent to which the patient had exposure were positive. The likelihood ratio calculation with a combination of tests showed that in a population with a 50% pretest probability a combination of

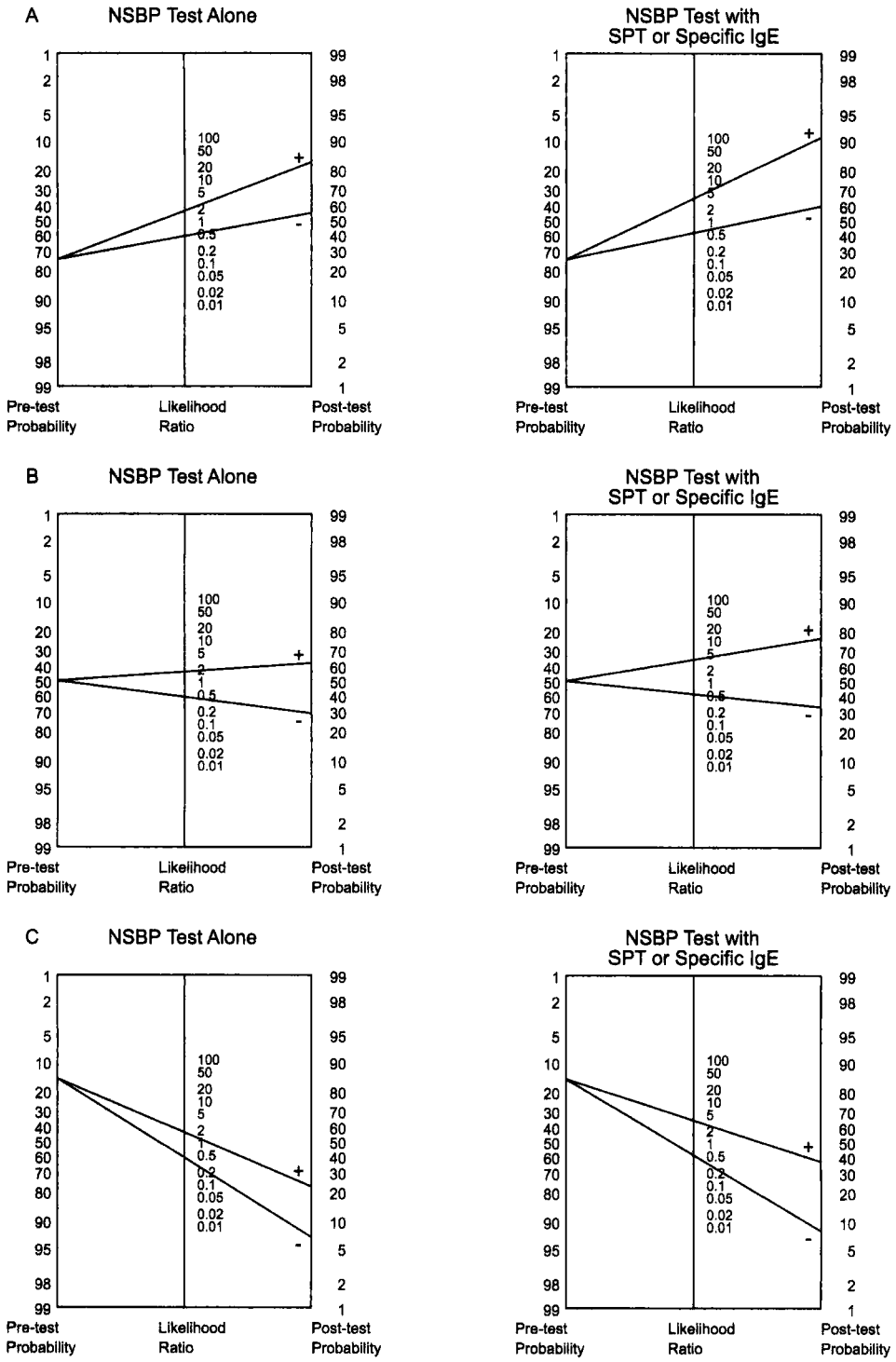

FIGURE 4. Nomograms depicting the effect of pretest probability of OA (from clinical history without objective tests) on the posttest probability of OA, using the examples of testing for nonspecific airway hyperresponsiveness by nonspecific bronchial provocation (NSBP) alone and in combination with an immunologic assay for specific IgE antibodies, by SPTs or *in vitro* tests. Reproduced with permission from Beach et al.[82]

positive test results adds to the posttest probability of sensitizer-induced OA (Fig 4).

In a study[85] of suspected sensitizer-induced OA patients, the addition of induced sputum cell counts showing an increase in sputum eosinophils during periods at work compared to away from work im-

proved the specificity of serial PEFRs by 18 to 26%, using SIC as the reference standard. Sensitivity was increased 8% with a cutoff level for increased sputum eosinophils of 1%, but was reduced with a cutoff level of 2%. This test is of no value, however, if the patient does not produce sputum during induction or cannot take time off from being in the suspected work area.[85–87]

For the exclusion of sensitizer-induced OA, a negative diagnostic test result, even a negative SIC response, is not always sufficient, and further diagnostic testing may be indicated (*eg*, serial PEFRs with or without methacholine testing or equivalent when on and off work).[1,88] The results of different tests may not be concordant, since all tests have potential false-positive and false-negative responses. The reasons include the following: intercurrent respiratory infections; medication changes; nonoccupational allergen exposures; variable exposures to the causative agent at work; and inadequate duration of time at work/off work to identify work-related changes in PEFRs. There can be a benefit from the repetition of such tests.

Most of the diagnostic tests providing objective evidence of work-relatedness are not relevant for those with suspected irritant-induced OA and are not included in the diagnostic criteria for that entity. They may be relevant, however, if it is suspected that the asthma-inducing exposure may also have caused sensitization (*eg*, from a spill of glutaraldehyde or diisocyanates).

WEA has been diagnosed most commonly by self-report of worsened asthma symptoms on the job in workers with preexisting asthma.[15,60,70] The use of qualitative or quantitative workplace exposure assessment, or "objective indicators" of asthma exacerbations such as a greater use of asthma medications, physician or hospital visits, or worsened pulmonary function (as determined by PEFRs, spirometry, and nonspecific airway responsiveness) has, to date, not been systematically reported.

Objective investigations for WRA are most feasible when the patient is still working. Therefore, workers should be investigated soon after the diagnosis is suspected and should be advised to remain in the same job until the diagnosis has been investigated, unless this is considered to be unsafe (*eg*, in the presence of severe symptoms). Ideally, patients with suspected WRA should be referred soon after suspicion of the diagnosis to a physician with expertise in the assessment of such patients.[89] A summary of the approach to diagnosis is included in Figure 2. Practical supplemental materials are also provided (www.chestjournal.org).

Panel Consensus

4. In individuals with suspected sensitizer-induced OA, in addition to carefully documenting the occupational history, perform additional objective tests when feasible (*eg*, serial PEFRs, serial methacholine challenges, immunologic assessments, induced sputum testing, and SICs) to improve the diagnostic probability.

Work-Related Changes in Physiologic Tests

Serial PEFRs in the Diagnosis of WRA

Most published reports[90] have examined lung function changes in patients with sensitizer-induced OA, and there are limited data on WEA. The use of "cross-shift" changes in lung function has had limited usefulness in diagnosing sensitizer-induced OA, probably in part due to late asthmatic responses occurring after the work shift.[91–94] Peak flowmeters provide a compact and inexpensive index of airway caliber. Portable flow-sensing spirometers, which have been more recently introduced, allow the measurement of FEV_1 and other indexes of airway caliber in a compact device,[95,96] although at greater expense than peak expiratory flow meters.

The advantages of PEFRs include device portability and the more realistic exposures that occur at work compared with the limited exposure testing available with SIC. Most studies of lung function testing in the diagnosis of sensitizer-induced OA have compared serial PEFRs with either SIC or an "expert diagnosis" of OA. The sensitivity and specificity of a PEFR in comparison with SIC can be high, with pooled estimates suggesting approximately 64% sensitivity (95% confidence interval, 43 to 80%) and 77% specificity (95% confidence interval, 67 to 85%).[11] Agreement of PEFRs with expert diagnosis has been reported,[97] with sensitivity and specificity of up to 75% and 94%, respectively, and a positive test result has been reported[98] to significantly influence expert opinion on the probability of sensitizer-induced OA.

Peak Flowmeter Considerations: Ideally, the peak flowmeter (or portable spirometer) should be simple, inexpensive, accurate, and reliable in use. Several peak flowmeters fit these characteristics. A patient should use the same type of peak flowmeter to reduce variability. Peak flowmeters may have a nonlinear response to changes in flow, and it is important to characterize the devices if possible.[99] Peak expiratory flow can be recorded in a standard diary, which can also be used to collect information such as the frequency of symptoms, medication use, and specific tasks at work. A data logger is a useful addition and is increasingly available; by recording the measurements, it prevents the possibility of

PEFRs being fabricated. Patients require a careful explanation of how to use the peak flowmeter, and there may be a learning effect during the first few days of use that can interfere with the interpretation.

Frequency and Duration of PEFRs: The optimal frequency and duration of PEFRs has not been fully established, although more frequent measurements over longer periods with good adherence to the test provide more information and increase sensitivity and specificity. One comparison of PEFRs made every 2 h with PEFRs made four times daily showed similar sensitivity and specificity in diagnosing sensitizer-induced OA,[100] with measurements made less than four times a day being less effective. A minimum of four readings daily seems necessary, with there being a possible benefit of obtaining readings more frequently. PEFRs should be performed throughout the day while the patient is awake, on days off work and at work.

The optimum duration of PEFRs has not been established, although a duration of several weeks is customary.[101,102] A prolonged period of testing is important as it may take several days or longer for workplace exposures to affect PEFR or for recovery to occur away from exposure. A recording period of 4 weeks, including a period of at least 1 week away from work, seems to be the minimum time necessary to reliably identify changes due to work (with optimally at least 2 weeks at work and $\geq$ 2 weeks off work). It may take repeated recording episodes to capture relevant exposures and changes in PEFRs. The absence of clear work-related changes does not exclude WRA (*ie*, sensitizer-induced OA or WEA).

Stability of Underlying Asthma and Use of Medication: The best time to identify changes in PEFRs from workplace exposures is when the patient with underlying asthma is as stable as possible. The use of long-acting bronchodilators or inhaled steroids may mask work-related changes, and a temporary switch to short-acting bronchodilators as needed or a reduced inhaled steroid dose may be required if PEFR monitoring is negative. Ideally, medication should remain unchanged throughout the recording period except for rescue medication, the use of which should be recorded. Intercurrent chest infections or exposure to asthma triggers away from work should be similarly recorded. Variable shift work may also cause problems in interpretation because of changes in the timing of diurnal rhythms of lung function.

Interpretation of Serial PEFRs: No single universally accepted technique for evaluating the results of serial PEFRs has emerged. Usually, the best of triplicate recordings made at each time point is taken as the value for that time. The results can be plotted (Fig 5) then visually interpreted to determine whether there is a pattern of worsened PEFRs during work weeks compared with days or weeks off work; when undertaken by "experts," there is relatively good agreement with the SIC in diagnosing sensitizer-induced OA.[103] The following various patterns can be seen: diurnal worsening during a work day that does not worsen progressively during the work week and improves on the weekend or other days off work; a diurnal pattern of worsening during the working day with the daily value before the work shift value falling progressively over the work week and worsening over successive weeks of work; and an intermittent fall in peak flows during working weeks with marked improvement after several days away from work. An alternative approach involves identifying asthma by the presence of significant diurnal variation in PEFRs (*ie*, a 20% fall in peak flow from maximum to minimum as the criterion) and then identifying the relative ratio of days with significant diurnal variation during work periods to the diurnal variation during days off work.[104] For example, for a 5-day work week, a significant diurnal variation occurring on 10 of 15 working days, on only 2 of 6 days off work on weekends, and 2 of 14 days off work would be a positive response. This technique gave a sensitivity of 93% and a specificity of 90% in diagnosing sensitizer-induced OA among those persons from whom PEFRs could be fully interpreted.[104] A more sophisticated method of analysis is based on a computer-generated discriminant analysis (OASYS-2; OASYS Research Group, Midland Thoracic Society; Birmingham, UK) that is commercially available and uses a different method of plotting results (Fig 6). It has also given reasonably good sensitivity and specificity of 75% and 94%, respectively, and relatively good agreement with the opinion of experts reading the plotted graphs (median κ value, 0.75).[93,97]

Limitations: While serial PEFRs have a number of advantages as a tool for diagnosing sensitizer-induced OA, they also have limitations. They are effort dependent and require good cooperation from the individual being investigated. PEFRs may be incomplete or uninterpretable for a variety of reasons.[105,106] Individuals may not be able to use the peak flowmeter or have difficulty in making PEFRs regularly over a prolonged period, despite training. By the time of referral, many patients already have left work or have been relocated to an area with reduced or no exposure, making it impossible to perform PEFRs at the same time as relevant expo-

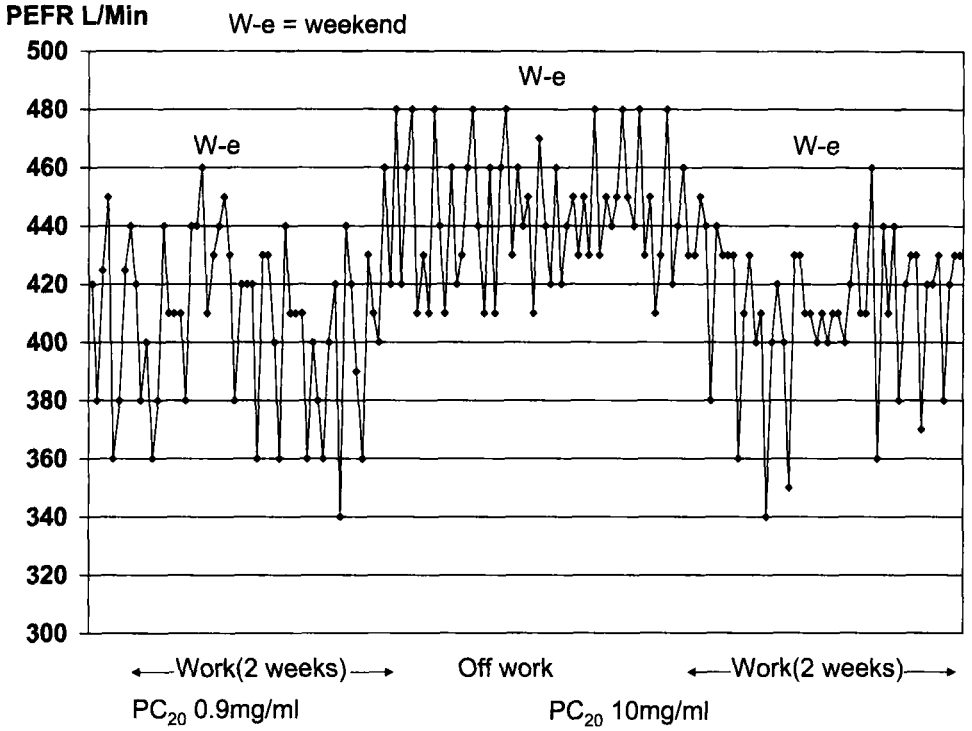

FIGURE 5. Peak flow OA example, illustrating significant variability in peak flows during work periods and little change over weekends off work, but improving while the patient was off work for several days. Methacholine challenge results also showed improvement in airway responsiveness at the end of the period off work compared to the period at work.

sures. For some workers, a period away from the relevant exposure is not feasible. Concerns about the falsification of results transcribed by patients can be partly overcome by using peak flowmeters with data loggers. PEFRs made in the workplace may be falsely negative if the causative agent is not in use at the time of testing. PEFRs cannot easily differentiate sensitizer-induced OA from WEA, as both may be associated with work-related changes in airway caliber (although some clues to a diagnosis of sensitizer-induced OA may be derived from the pattern of changes). In addition, PEFRs are rarely useful in the setting of irritant-induced asthma, as it is usually not possible or desirable to recreate the same type of exposure that initially caused the symptoms. Finally, even if PEFR results are positive, it may not be possible to identify a specific causative agent. Despite these limitations, serial PEFRs can be useful as part of the diagnostic workup in those persons who still have the relevant work exposure.

Panel Consensus

5. In individuals with suspected WRA who are currently working at the job in question, record serial measurements of peak flow as part of the diagnostic evaluation and ask the patient to record these optimally a minimum of four times daily for at least 2 weeks at work and 2 weeks off work.

Serial Measures of Airway Responsiveness in the Diagnosis of WRA

Statements and reviews for the diagnosis of sensitizer-induced OA[74,83,88,107] have suggested that a methacholine or histamine challenge be performed toward the end of a work week and be repeated at the end of a period (usually ≥ 10 to 14 days) away from the exposure, and that a worsening of the provocative concentration of a substance causing a 20% fall in FEV_1 (PC_{20}) at work vs off work beyond the normal variability of the test (defined[107] as a threefold or greater change in PC_{20}) would provide additional evidence to support the diagnosis of sensitizer-induced OA.[83] A smaller shift in PC_{20} would be less definitive in the diagnosis. The basis of this suggestion has been the observation that with exposure to a work sensitizer, a positive response is often associated with an increase in nonspecific airway hyperresponsiveness compared with preexposure results.[108]

Both methacholine and histamine inhalation challenge testing[109–113] have been used in this manner.

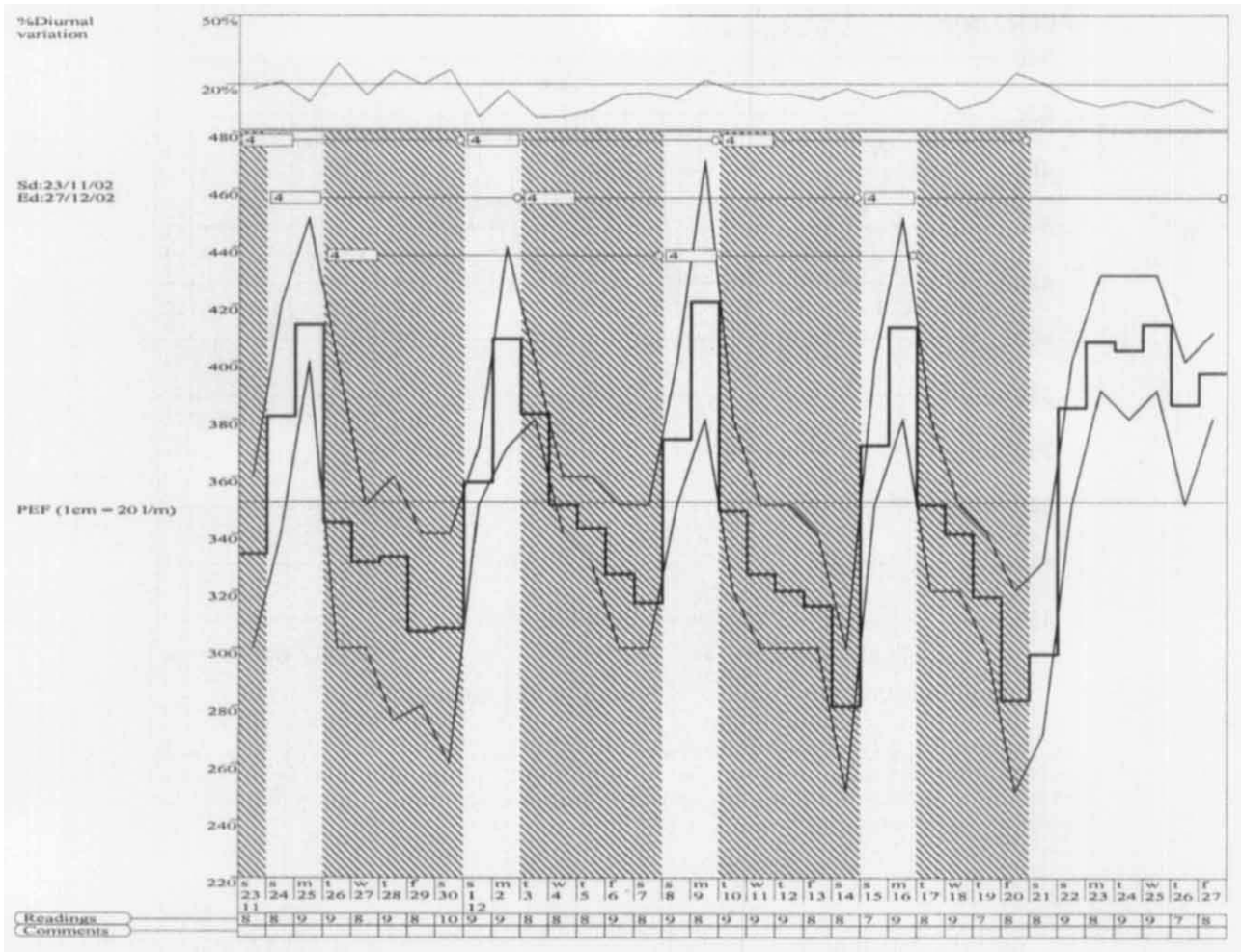

FIGURE 6. PEFR from a patient with OA, plotted using the OASYS system (OASYS Research Group, Midland Thoracic Society). Minimum, mean, and maximum daily PEFRs are plotted. The mean is the stepped line with minimum and maximum below and above, respectively. Each day is shown on the x-axis, and peak flow is shown on the y-axis. Days at work are shown hatched. Deterioration in the patient's condition is seen on days at work, with recovery each weekend, which is sustained in the longer period away from work at the end of the PEFR. Numbers in small boxes with lines on the graph show OASYS 2 scoring for each rest/work/rest or work/rest/work period. *Top*: diurnal variation on each day. *Bottom*: number of recordings each day.

The tests should be performed using standard recommended protocols and methods[114–121] supported by European and North American respiratory societies.[120,122,123] Changes in airway hyperresponsiveness are best evaluated by comparing tests conducted in the same laboratory.

Patient-related factors that impact results include the actual degree of airway responsiveness as well as other factors. The failure to discontinue bronchodilator therapy for an adequate time interval before the test will reduce the measured responsiveness; the effects of current inhaled corticosteroids are less marked (a mean reduction of approximately one doubling dose).[124] A respiratory infection within the 6 weeks prior to testing can increase airway responsiveness.[125] Repeat tests are best compared when the baseline FEV_1 is similar. Exposure within days to weeks before the test to a nonoccupational allergen to which the patient is sensitized can increase airway hyperresponsiveness.[126,127] Gastroesophageal reflux disease may also impact the results.[128] Such factors must be considered when evaluating changes in responsiveness during periods on and off work. In addition, workers with longstanding OA from a sensitizer to which they are still exposed may have airway remodeling and less acute improvement in airway responsiveness once removed from the work sensitizer. Such patients may have slow improvements in lung function over months or even years away from work.[126,127]

Although studies[85,101] have found serial changes in methacholine or histamine responsiveness to be

useful as part of the diagnosis of sensitizer-induced OA, few have assessed sensitivity and specificity in comparison to SIC. A study[101] designed mainly to compare serial PEFRs with SIC reported a lower sensitivity and specificity of serial methacholine challenges. Another report[85] noted serial methacholine challenges to be less sensitive and specific compared with SIC. The AHRQ review[11] failed to identify sufficient evidence comparing serial measures of nonspecific airway responsiveness in patients with OA compared with SIC to provide a conclusion on effectiveness. As might be expected, the review did demonstrate a good relationship between positive SIC findings and a single positive methacholine test result. Both a positive methacholine test result and a change with work exposure have been reported[98] to significantly influence expert opinion for a high-probability diagnosis of OA. In contrast, a methacholine challenge result can revert to normal away from exposure and can be normal in a worker with OA who then has a positive SIC finding.[129] There have been a few case reports of negative methacholine challenge results in patients soon after an SIC finding that is positive for diisocyanates,[130] but this appears to be a rare occurrence. Some agents responsible for WEA (*eg*, common allergens at work and to a lesser extent agents such as ozone[131]) may also cause some work-induced changes in airway responsiveness, and an improvement in methacholine responsiveness off work has been reported[85] in those who have WEA in whom sensitizer-induced OA was excluded by SIC. A patient with irritant-induced OA would not be expected to have significant worsening of airway hyperresponsiveness on a return to work. In summary, despite inadequate numbers of studies to allow formal evidence-based analyses to assess the sensitivity and specificity of serial testing of nonspecific airway responsiveness[11] for the diagnosis of sensitizer-induced OA, the available literature and clinical experience supports the use of this method when carefully performed as an additional approach to document functional airway changes related to workplace exposures.

Panel Consensus

6. In individuals with suspected sensitizer-induced OA, working at the job in question, conduct a methacholine challenge test or a comparable measure of nonspecific airway responsiveness during a period of work exposure and repeat it during a period (optimally, at least 2 weeks) away from the work exposure to identify work-related changes.

Specific Immunologic Testing

OA and rhinitis caused by HMW proteins in the work environment are associated with specific IgE antibody production. SPTs detect tissue-bound IgE antibodies, and are highly sensitive and specific for identifying a specific IgE antibody response to protein allergens.[132,133] When the results are positive in a worker with a history of sensitizer-induced OA and documented asthma, a positive SPT response to an allergen that is present at work helps to identify a suspected cause and supports a diagnosis of sensitizer-induced OA. The demonstration of decrements in lung function associated with exposure further improves diagnostic certainty.[132,133] Due to a high NPV, a negative SPT response to a validated occupational protein allergen test reagent can exclude sensitizer-induced OA due to that allergen with a high degree of accuracy.[132,134] An important practical limitation is the general lack of standardized commercial skin test reagents for many occupational proteins. Exceptions include standardized natural rubber latex (NRL) [available in Europe] and standardized cat dander or pelt diagnostic extracts and venom from stinging insects (relevant for beekeepers). Nevertheless, nonstandardized commercial reagents are widely available and can be used for SPTs of food (*eg*, wheat, rye extracts) and laboratory animals (*eg*, mouse, rat, and guinea pig). SPTs with a panel of common aeroallergens can be useful in the evaluation of suspected WRA to help determine the contribution of such allergens and for differentiating WRA from chronic asthma symptoms triggered by inhaled allergens outside the work environment (*eg*, household pets).

Specific IgE antibodies have not been consistently associated with most chemical (*ie*, LMW) causes of sensitizer-induced OA, and therefore skin testing or *in vitro* testing for specific IgE antibodies to such chemicals is usually not indicated. Test antigens that have been utilized for assessing sensitization to LMW chemicals are usually prepared and characterized in individual research laboratories, and are not generally commercially available.[135,136]

Performance of Immunologic Testing in Sensitizer-Induced OA: The diagnostic utility of immunologic tests compared to SIC has been addressed in the AHRQ review,[11] which concluded that specific immunologic testing for sensitizer-induced OA is a useful diagnostic test when feasible. Table 7 provides details on some studies[54,132–135,143,148–150,152,300–304] of the performance of these tests for different sensitizers.

HMW (Protein) Allergens at Work: SPTs are considered to be more sensitive than US Food and

Table 7—*Examples of Studies Which Illustrate Test Performance of Immunologic Tests for Agents Relevant to Diagnosis of OA in Selected Populations*

Study/Year	Allergen	Test	Population	Subjects	"Gold Standard" Test	Sensitivity for OA, %	Specificity for OA, %
Vandenplas et al[132]/2001	Nonammoniated NRL (Stallergènes SA; Antony, France)	SPT	HCWs with possible OA, Pharmaceutical workers, and food processors	45 workers: SIC-positive, 31 workers; SIC-negative, 14 workers	SIC	100	21
Quirce et al[54]/2003	Nonammoniated NRL (total protein, 400 μg/mL)	SPT	HCWs with history of latex asthma	30 subjects: SIC-positive, 19 subjects; SIC-negative, 11 subjects	SIC	100	20
	Pharmacia CAP (Phadia AB; Uppsala, Sweden)	RAST				95	40
Koskela et al[133]/2003	Commercial bovine extract (1:100 w/v)	SPT	Dairy farmers with history consistent with OA	37 subjects: SIC-positive, 11 subjects; SIC-negative, 26 subjects	SIC	100	50
	Bovine IgE-RAST (UniCAP diagnostic system)	RAST				82	100
Merget et al[134]/1993	Industrial enzymes (concentration, 10 mg/mL): Amylase; Papain; Pectinase; Cellulose; Amyloglucosidase; Hemicellulose	SPT	Chemical plant workers with work-related symptoms	42 subjects: SIC-positive, 13 subjects; SIC-negative, 29 subjects	SIC	100	93
	Industrial enzyme solution	IgE-RAST				62	96
Fernandez et al[300]/2007	Cat, 100 BU/mL (ALK-ABELLÓ; Hørsholm, Denmark); fel d 1, 40 μg/mL	SPT	Patients with asthma and unclear association with cat allergy	64 subjects: SIC-positive, 27 subjects (42%; SIC-negative 37 subjects (58%)	SIC	89	19
	1, 0.1, and 0.01 BU/mL	ID				96	34
	CAP-FEIA (Pharmacia Diagnostic; Freiburg, Germany)	IgE-RAST				96	33
Choudat et al[301]/1999	Wheat	SPT	Baker syndrome with symptoms suggestive of OA	21 subjects: SIC-positive, 12 subjects; SIC-negative, 7 subjects; not done, 2 subjects	SIC	93	71
	CAP (Pharmacia Diagnostic)	IgE-RAST				100	57
Sander et al[302]/2004	Wheat: ALK; Bencard	SPT	Bakers with work-related respiratory symptoms	115 subjects: SIC with wheat, 51 subjects; SIC with rye, 69 subjects	Wheat: ALK SPT, 51 subjects (SIC-positive, 29 subjects)	45	86
					Wheat: Bencard SPT, 45 subjects (SIC-positive, 24 subjects	67	90
	Rye: ALK; Bencard	SPT			Rye: ALK SPT, 69 subjects (SIC-positive, 48 subjects)	40	95
					Rye: Bencard SPT, 53 subjects (SIC-positive, 38 subjects)	50	100
	Wheat and rye: Phadezym	IgE-RAST				83 72	59 81

(*Continued*)

Table 7—*Continued*

Study/Year	Allergen	Test	Population	Subjects	"Gold Standard" Test	Sensitivity for OA, %	Specificity for OA, %
Munoz et al[303]/2004	Ammonium persulfate salt	SPT	Hairdressers with symptoms, 8 subjects; unexposed asthmatic patients, 8 subjects	16 subjects: SIC-positive, 9 subjects; SIC-negative, 7 subjects	SIC	44	100
Park et al[148]/2001	Vinyl sulfone dyes: Remazole black GR; Orange 3R	SPT 10 mg/ml, 0.4% phenol, 0.9% NaCL, 50% glycerin	Exposed dye workers: OA, 42 subjects; no symptoms, 93 subjects; unexposed, 16 subjects	151 subjects: SIC-positive, 42 subjects; SIC-negative, 109 subjects	SIC	76	91
	Black-HSA; Orange-HSA	ELISA-IgE				54	86
Shirai et al[143]/2003	Green tea (epigalloca-techin gallate)	ID ≤ 1 mg/mL in NS solution	Tea workers with symptoms	21 subjects: SIC-positive, 11 subjects; SIC-negative, 10 subjects	SIC	100	80
Cartier et al[135]/1989	Diisocyanates-HSA conjugates	ELISA-IgE	Exposed workers with symptoms	62 subjects: SIC-positive, 29 subjects; SIC-negative, 33 subjects	SIC	28	97
		ELISA-IgG				72	76
Tee et al[150]/1998	Diisocyanates-HSA (TDI)	RAST IgE ≥ 2 (Phadebas; Cambridge, MA)	Exposed workers with symptoms	70 subjects: SIC-positive, 46 subjects; SIC-negative, 24 subjects	SIC	28	92
Ye et al[136]/2006	Vapor TDI-albumin	IgE-ELISA	Challenge-positive, 66 subjects; Exposed asymptomatic workers, 167 subjects	233 subjects	SIC for positive OA diagnosis	44	96
		IgG-ELISA				30	90
Park et al[304]/1999	TDI-HSA	ELISA-IgE	Exposed workers	63 subjects: SIC-positive, 50 subjects; SIC-negative, 13 subjects	SIC	14	92
		ELISA-IgG				46	92
Merget et al[149]/1991	Complex platinum salts, 10^{-2} to 10^{-8} mmol/L $PtCl^{6\,2-}$ (Sigma; St. Louis, MO)	SPT	Workers with work-related symptoms, unexposed asthma control subjects	36 subjects: SIC-positive, 22 subjects; SIC-negative, 14 subjects	SIC	82	93

*Several study populations are small and results presented should be interpreted in this context. Populations without OA did not have the "gold standard" test in all studies. For agents used in SPTs where the extracts were tested, in general these SPTs were more sensitive than *in vitro* tests. HCW = health-care worker; ELISA = enzyme-linked immunosorbent assay; TDI = toluene diisocyanate.

Drug Administration-approved, *in vitro*, specific IgE antibody assays[83,137] for assessing clinically relevant specific IgE antibodies to most HMW proteins (*eg*, NRL), showing up to 100% sensitivity (and 21% specificity) for health-care workers with NRL-induced OA confirmed by SIC.[132] Similarly, among industrial enzyme workers, SPTs with enzyme solutions showed 100% sensitivity (and 93% specificity) vs 62% sensitivity (96% specificity) for a serum allergosorbent enzyme-specific IgE antibody assay.[134] Sensitized workers may have falsely negative SPT or RAST responses to HMW occupational allergens if they are tested after not being exposed for a prolonged period (a half-life of 20 to 21 months has been estimated for serum IgE antibodies to detergent enzymes[138]).

LMW (Chemical) Antigens in the Workplace: Several chemical agents known to cause sensitizer-induced OA have been associated with specific IgE

antibodies including the following: acid anhydride compounds (*eg*, trimellitic anhydride,[139] phthalic anhydride[140]); chloramine-T[141]; persulfates[142]; epigallocatechin gallate[143]; vinyl sulfone reactive dyes[144]; and platinum salts.[145] Nonetheless, few studies have attempted to validate SPTs with these chemicals as diagnostic tests for OA, and the sensitivity is typically lower than with HMW proteins. Protein conjugates are formed with chemical haptens *in vivo* by combining them with autologous proteins[146] such as human serum albumin (HSA), which can be used as test antigens. This process may not be applicable to all chemical sensitizers. SPT responses to anhydride-HSA conjugates were detected in 50% of anhydride-exposed workers with confirmed sensitizer-induced OA,[147] and among reactive dye manufacturing workers, SPT responses to vinyl sulfone dye solutions exhibited 76% sensitivity (91% specificity) for confirmed sensitizer-induced OA.[148] SPT responses to hexachloroplatinate salts have been reported in 82% of platinum refinery workers with confirmed sensitizer-induced OA.[149]

The association of diisocyanate asthma with serum-specific IgE and IgG antibodies reactive with chemical-HSA antigens has been extensively investigated. IgE antibodies specific to diisocyanate-HSA conjugates have been detected in 21 to 55% of cases of diisocyanate-induced OA confirmed by SIC or workplace challenge in different studies,[136,150,151] with an assay specificity of 89 to 100%. Diisocyanate-specific IgG antibodies appear to be a good marker for recent diisocyanate exposure, rather than diisocyanate asthma, since they can be detected in a substantial proportion of asymptomatic exposed workers.[136,151,152] Active exposure to diisocyanate increases the sensitivity and specificity of specific IgE antibodies reactive with diisocyanate conjugate by RAST. The detection of diisocyanate-specific IgE antibodies fell if assayed ≥ 30 days after the cessation of occupational exposure, with a calculated half-life of 5 to 7 months.[150]

The clinical data examining *in vitro* antigen-specific cellular immune responses to establish a diagnosis of chemical sensitizer-induced OA are limited. *In vitro* proliferative responses to plicatic acid-HSA antigen have been demonstrated in 24% of workers with red cedar-induced asthma, compared to 0% in exposed workers without red cedar-induced asthma. *In vitro* monocyte chemotactic protein-1 production by mononuclear cells cocultured with diisocyanate-HSA antigens[153] exhibited 79% test sensitivity and 91% specificity for the diagnosis of OA compared with SIC results among 54 exposed workers.

Current Limitations of Immunologic Testing: There are several limitations to immunologic testing for determining a patient's sensitization to LMW chemical agents. Antigens are prepared by conjugating chemicals with a protein such as HSA; however, the chemical-protein conjugate antigens and protocols have not been standardized, and results cannot be compared between laboratories.

Test extracts for most HMW proteins that cause OA are not commercially available and are frequently prepared differently by different investigators. Commercial extracts, if available, may not be standardized with regard to allergenic potency. The test sensitivity of *in vitro* specific IgE antibody assays and SPTs likely decrease after the cessation of exposure due to the half-life of the IgE antibody. Immunologic testing with validated allergens can identify work-acquired sensitization; however, a negative test result would not exclude sensitization to a different workplace agent. There is little published information on the PPVs and NPVs of these tests among working populations. Common allergens such as dust mites, cat dander, or fungal spores (present above background levels in some working environments) can trigger WEA in persons with atopic asthma who have been sensitized to these agents, and SPTs with the appropriate allergen extracts can support this diagnosis. Immunologic testing is not helpful in identifying WEA due to nonallergic work triggers and is not indicated for the detection of irritant-induced asthma.

Panel Consensus

7. In individuals with suspected sensitizer-induced OA, conduct immunologic testing (skin prick testing or *in vitro* specific IgE assays) to identify sensitization to specific work allergens when the tests are technically reliable and available.

SIC

SIC involves exposing workers who are suspected of sensitizer-induced OA to suspected agents in a safe and controlled fashion. SIC is intended to demonstrate a direct relationship between exposure to a test agent and an asthmatic response. The SIC has often been referred to as the "gold standard" for the diagnosis of sensitizer-induced OA; however, the AHRQ review[11] concluded that "as yet there is no definitive diagnostic test for OA," and considered SIC to be a "reference standard" rather than the "gold standard." Another guideline on OA[20] concluded, based on expert opinion, that the SIC "comes closest to a gold standard test for some agents causing (sensitizer-induced) OA." While it is a useful research and diagnostic test, SICs are performed in only a few centers in the world, require

specialized facilities and expertise, and generally are not available in the United States and many other countries.[154]

SIC procedures have been described in textbooks and review articles.[155,156] Briefly, a challenge chamber or closed-circuit apparatus can be used to generate and monitor the suspected agent.[118,156–160] The type of exposure varies according to the occupational agent (*eg*, protein, chemical, or water-soluble agent) and the work usage, with an attempt made to mimic the work exposure.[161] The worker can also perform a simulated work task in a monitored laboratory environment, in the "realistic method."[85,156] With any type of exposure, a control day, during which the stability of the asthma patient is assessed, is performed first followed by the exposure days, which can take several days to complete.[85]

SICs have been invaluable in confirming the capacity of new workplace agents to cause sensitizer-induced OA, characterizing well-defined groups of patients for clinical studies, and aiding research into pathogenesis. The SIC can confirm the diagnosis of sensitizer-induced OA when the findings of other testing have been inconclusive, can make the diagnosis more expeditiously, or can identify the specific agent if the worker is exposed to more than one OA-causative agent.[22,83]

However, there are several limitations to the SIC. There are practical considerations, such as the need for highly specialized facilities and trained staff, and the substantial costs and time involved.[162] In addition, SICs are not useful in diagnosing irritant-induced asthma or WEA. Furthermore, false-positive and false-negative responses to an SIC can occur.[83,163,164] Although not common, false-positive responses can be seen in unstable patients with asthma, in patients with marked airway hyperresponsiveness, or in patients with inadvertent exposures to irritating levels of an agent.[164] False-negative responses can occur for a number of reasons. Workplace exposures, which can be mixed, complex, and nonuniform, can be difficult to characterize and simulate. Exposure to the wrong agent or process, an inadequate concentration or timing of the exposure, a loss of specific airway responsiveness away from exposure, or the use of medications to treat asthma can all result in false-negative responses.[162,165–167] Measuring airway responsiveness before and after challenges may reduce the number of false-negative tests by detecting changes in airway responsiveness even without changes in FEV_1, warranting further challenge testing (*ie*, additional challenge days or higher dose) to identify positive responses.[168,169] Since SIC has been taken as the reference standard for diagnosis, there are no studies that have analyzed the PPV and NPV for this test.

Workplace Challenges: When a specific agent cannot be identified as a potential cause for sensitizer-induced OA, a subject is exposed to several potential sensitizers, the exposure cannot be reproduced in the laboratory, or an SIC in a laboratory setting is not available, an inhalation challenge may be undertaken in the field at the workplace. This challenge, termed *workplace challenge testing*, consists of monitoring spirometry at the workplace when the subject performs the task that is suspected to cause sensitizer-induced OA. Like SIC conducted in the laboratory, SIC conducted at the workplace is preceded by a control day that is performed in the laboratory (without simulated exposure), or at another job at the workplace that does not involve the exposure in question, to evaluate the baseline variability in FEV_1.

Panel Consensus

8. In individuals with suspected sensitizer-induced OA, conducting SIC (where available) is suggested when the diagnosis or causative agent remains equivocal; however, this testing should only be performed in specialized facilities, with medical supervision throughout the testing.

Emerging Diagnostic Tests: Noninvasive Measures of Airway Inflammation

Sputum induction and the sampling of exhaled breath (gases and condensates) provide noninvasive approaches to assessing the cellular and biochemical environment of various compartments of the lungs that have been helpful for the diagnosis and management of chronic asthma. More recently, these have been assessed for the investigation of WRA, mainly sensitizer-induced OA.

Induced Sputum Cell Counts: This method consists of inducing sputum production by the inhalation of nebulized hypertonic saline solution, processing the sample, and preparing slides from it that are stained for differential cell counts.[170] Induced sputum analysis has been used to support the diagnosis of OA preceding and following SIC in the laboratory[87,171] or at the workplace,[85,86] although it currently remains a tool with limited availability.

Sputum eosinophils increase after exposure to both HMW agents[19,87] and LMW agents such as diisocyanates,[172] red cedar,[171] or cyanoacrylates.[173] In some cases, an exposure is followed by sputum neutrophilia (*eg*, after exposure to diisocyanates,[174–176] metal working fluid,[177] and grain dust[178]). Factors that influence the type of inflammatory responses are un-

clear but may include the type of asthmatic reaction and the intensity of airway inflammation induced.[176]

Subjects with possible WRA have been investigated while at work and when away from work for at least 2 weeks.[86] Sputum eosinophilia developed in subjects with sensitizer-induced OA while at work and resolved when subjects were away from work. Asthma patients without OA did not show changes in airway inflammatory parameters. A study[179] of sensitizer-induced OA due to LMW agents identified 37% of the 38 patients as having sputum eosinophil counts of > 2.2% while they were still being exposed at work. Both eosinophilic and noneosinophilic OA groups demonstrated high sputum neutrophil counts of > 50%. The presence of sputum eosinophilia in this study did not relate to the causative agent, the duration of exposure, atopy, or a lack of treatment, but was associated with more severe disease. Another study[85] assessed whether induced sputum cell counts performed with the subject at work and away from work could improve the diagnosis of sensitizer-induced OA when combined with PEFR monitoring and compared with SIC findings. The addition of sputum cell counts (with a cutoff value of > 1% or a > 2% increase in eosinophils when the subject was at work, compared to results when the patient was away from work) improved the specificity for the diagnosis of sensitizer-induced OA (by 18% or 26%, respectively).[85] Additional studies have suggested a possible role for induced sputum in the early diagnosis of sensitizer-induced OA, even before the occurrence of respiratory symptoms and pulmonary function changes,[180] and as an additional marker of respiratory impairment[181] and persistent airway inflammation after changing jobs.[182]

Exhaled Breath Nitric Oxide: In patients with active asthma, exhaled nitric oxide (ENO) levels are elevated, and the levels fall after steroid therapy.[183,184] Laboratory and workplace studies have shown increases in ENO levels even in nonasthmatic patients that are related to exposures such as ammonium bisulfate,[178,185] the aluminum smelter potroom workplace,[186] pulp-mill gassing incidents,[187,188] and in leather workers who have been exposed to solvents.[189] In contrast, there was no significant increase in ENO levels postexposure among healthy workers in a swine confinement building.[190] Underground workers, especially those with respiratory symptoms, exposed to particulate matter and nitrogen dioxide, showed elevated levels of ENO compared to outdoor workers,[191] despite a lack of differences in spirometric findings between these two groups.

Limited numbers of studies have examined the changes of ENO levels in patients with sensitizer-induced OA. Asthma among laboratory animal workers was associated with higher ENO levels compared to asymptomatic laboratory animal workers.[192] Another study[193] found no clear relationship between either positive SIC or elevated specific IgE antibody response and an increase in ENO levels. Among health-care workers, latex-sensitized workers showed increased ENO levels at 22 h after a latex challenge,[194] which was significantly related to airflow limitation, though an earlier study[195] had not shown changes with workplace latex exposures. In a group of 40 workers, ENO levels were significantly increased after a positive SIC response in those workers with normal or slightly increased prechallenge ENO levels.[196] After an SIC with diisocyanates, an increase in ENO levels was more likely to develop in challenge responders with baseline airway hyperresponsiveness compared to nonresponders.[197]

Exhaled Breath Condensate: Exhaled breath condensate (EBC) likely contains aerosolized droplets of airway lining fluid and volatile compounds,[198–201] including hydrogen peroxide, aldehydes, leukotrienes, prostaglandins, F2-isoprostanes, cytokines, antioxidants, glutathione, and nitrosated species.[202–213] Studies[214,215] have reported inconsistent levels of these compounds in EBC, and this topic has been addressed in an American Thoracic Society/European Respiratory Society Task Force.[216,217] We are not aware of studies utilizing EBC in OA patients.

In summary, the use of noninvasive measures of airway inflammation for the investigation of WRA is promising. Induced sputum cell counts may add useful information to the diagnostic process. There is limited evidence for the use of ENO levels as an additional tool in the investigation of sensitizer-induced OA. Further research needs to be conducted to establish the usefulness of these tests in the diagnosis and management of OA.

Management of WRA

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, dividing it into the modification

of exposure, follow-up, compensation, medications, immunotherapy, and financial consequences to the worker.

The AHRQ review[11] concluded that better outcomes occurred in those with sensitizer-induced OA patients who left work vs those who remained at work. An avoidance of further exposure to the work sensitizer can be achieved by the complete elimination of the agent from the workplace (*eg*, diisocyanates from the work process[218]) or the removal of the worker with sensitizer-induced OA from the causative exposure (*eg*, from platinum salts or toluene diisocyanate[219,220]). Removal from exposure has been shown to have a beneficial effect with respect to both symptoms and pulmonary function,[221,222] though significant rates of depression and anxiety (50%) have been reported.[222] However, economic concerns may compel some individuals with sensitizer-induced OA to remain exposed. Continued exposure after diagnosis has been associated with a worsening of symptoms and outcomes,[7] including lower FEV_1 measures,[223] even when more medications were used.[224]

Reduced exposure is another treatment option. A beneficial effect was observed when workers with sensitizer-induced OA due to platinum salts were transferred to low-exposure areas of the company.[219] Health-care workers with OA from NRL have been able to safely return to work in settings where they avoid the personal use of NRL products, and where coworkers use powder-free, low-protein gloves.[225] However, placing workers with toluene diisocyanate-induced asthma in environments with low-level exposures has not been as successful[226]; overall, there is limited evidence for using this approach.[11]

Continued exposure may lead to greater airway inflammation and potentially more airway remodeling[182] and lower FEV_1.[223] When patients are unwilling or unable to leave a job, the initiation of antiinflammatory and bronchodilator therapy may be the only management option available to the clinician, although the patient should be educated to understand that continued exposure may lead to a worse outcome; it is essential that patients have careful medical monitoring so that any worsening of asthma can be detected early and further interventions applied. Similarly, close monitoring is needed if patients continue to be exposed to a relevant work sensitizer while awaiting the outcome of a compensation claim.

Management of Irritant-Induced OA

Limited data exist on the effect of the cessation of exposure in patients with irritant-induced OA. One report[227] of three patients with repetitive exposure to irritants at work suggested a benefit for removal from the exposure. Unlike workers with sensitizer-induced OA, however, 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 agent 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.

Management of WEA

The literature on the natural history and management of patients with WEA is limited, and the factors that predict worse outcomes are not well defined. These studies should be interpreted with caution due to varying diagnostic criteria, health and economic end points, and comparison groups. Very few studies to date have evaluated different treatment or preventive strategies in WEA patients, but bar workers with asthma had reduced airway inflammation and improved quality of life after the implementation of smoke-free environment legislation.[228]

Panel Consensus

9. For all individuals with WRA, attempt better control of exposures. Remove patients with sensitizer-induced OA from further exposure to the causative agent in addition to providing other asthma management.
10. In individuals with irritant-induced asthma or WEA, the panel advises optimizing asthma treatment and reducing the exposure to relevant workplace triggers. If not successful, change to a workplace with fewer triggers is suggested in order to control asthma.

Prognosis of OA

The long-term consequences of OA are variable and require prolonged follow-up. For example, the AHRQ review[11] of sensitizer-induced OA demonstrated continued improvement of lung function, often requiring follow-up durations of > 2 years. Moreover, prolonged follow-up has also been required to demonstrate improvement in nonspecific airway responsiveness. A systematic review of the outcome of sensitizer-induced OA[229] reported

a pooled estimate of symptomatic recovery of 32%, varying from 0 to 100% 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. Outcomes were best in those patients with a shorter duration of exposure. 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.

Pharmacologic Treatment of WRA

The pharmacologic treatment of OA and WEA does not differ from the treatment of other types of asthma and relies on a stepwise approach according to the severity of asthma and asthma control, as defined in the Global Initiative for Asthma guidelines.[29,30]

Pharmacologic Treatment in OA: There are very few studies that have specifically examined pharmacologic treatment in the management of OA. The AHRQ review[11] identified only 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. Since that time, one additional trial has been identified.[175] The methodological quality of all of these trials was low, the sample sizes were small, and dissimilar populations and interventions precluded metaanalytic synthesis.

Inhaled Corticosteroids

Two double-blind, placebo-controlled studies[230,231] compared the efficacy of inhaled beclomethasone to placebo in subjects with sensitizer-induced OA who were withdrawn from their occupational exposure. Significant improvement in PEFRs, quality of life, or airway hyperresponsiveness was found in the randomized double-blind crossover study[230] of 32 subjects when the subjects were treated with beclomethasone for 6 months after the cessation of exposure, compared with treatment with placebo. The other double-blind study[231] of parallel groups who were treated for 5 months showed improvement in their response to methacholine at the end of the active treatment vs treatment with placebo, but no change in specific responsiveness to the causative agent (diisocyanates). Therefore, it seems beneficial to initiate an early treatment with inhaled corticosteroids in subjects with sensitizer-induced OA in addition to removal from exposure.

Other Antiinflammatory Agents

Therapy with omalizumab[232] decreased conjunctivitis symptoms in latex-sensitized health-care workers, but the effect on asthma was not reported.

Other Medical Regimens Used During SICs: Studies have assessed the effect of medications on asthmatic responses and airway responsiveness induced by various occupational sensitizing agents (mainly diisocyanates and flour) during SICs in subjects with sensitizer-induced OA.[233–237] Although these data bring additional information on pathophysiology, they have a limited impact on the pharmacologic management of patients with sensitizer-induced OA.

Overall, the evidence on this issue is weak, and conclusions regarding the effectiveness of medications in managing OA are difficult to draw. Many of the trials suffered from a limited duration of treatment and dissimilar comparisons. The effectiveness of the medications studied among workers with sensitizer-induced OA appeared to be similar to that of others with chronic asthma.

Management of OA by Immunotherapy: 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.[238] Immunotherapy could be considered in settings where OA due to a specific allergen has been established, when only one or a few allergens have been linked clinically to disease, when the avoidance of the triggering allergen is impossible, and when there is a standardized allergen extract available for treatment. 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 nonoccupational allergens, or by the sublingual route, for which there is less information about efficacy especially with occupational allergens. Systemic reactions to immunotherapy are less frequent with the sublingual approach.[239]

There have been a limited number of studies of immunotherapy with allergens of potential occupational relevance. These include NRL for health-care workers, venom from stinging insects for beekeepers, wheat for bakers, grass or ragweed pollen for outdoor workers, and cat allergen for animal workers. Subcutaneous immunotherapy for exposure to NRL has been shown to be effective in reducing workplace symptoms, specific skin reactivity, and medication use,[240,241] but has not yet been shown to improve the clinical course of OA.[242,243] Systemic re-

actions to NRL immunotherapy were frequent, but not severe. Sublingual NRL immunotherapy has similar effects,[244,245] but anaphylaxis occurred with higher doses.[245]

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[246–251] who are at risk for future stings. A study[252,253] of bakers with asthma who were treated with flour immunotherapy showed decreased skin reactivity to flour, lower nonspecific airway responsiveness, lower serum wheat flour IgE antibody levels, and marked subjective symptom improvement compared to control subjects to whom placebo was given.

Few studies have evaluated the efficacy of immunotherapy for laboratory animal allergy, compared to the many studies for pet allergy. In patients with nonoccupational cat allergic asthma, immunotherapy with the major cat allergen Fel d1 is effective in mitigating symptoms of asthma and rhinoconjunctivitis and decrements in lung function.[254–256] No similar studies have been conducted in animal workers (*eg*, researchers and veterinarians), but, based on evidence supporting efficacy and safety in allergic asthma, cat immunotherapy may be advised for workers with unavoidable intermittent work-related exposure to cats.

In summary, in the absence of good control with pharmacotherapy and inability to completely avoid the allergen, and where validated extracts are available, immunotherapy for occupational allergens could be an effective treatment of allergy to and asthma from HMW antigens in work environments. Immunotherapy 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. In nonoccupational environmental settings, immunotherapy has been shown[257–259] to prevent progression from rhinitis to asthma, and thus has the potential ability to alter the natural history of the disease; however, there is no evidence for this as yet in patients with OA. Immunotherapy is not indicated to treat irritant-induced asthma. In individuals with sensitizer-induced OA due to selected HMW agents, immunotherapy may be an effective management option when a commercial extract is available and the causative agent cannot be completely avoided for economic, professional, or other reasons.

Socioeconomic Outcomes

The AHRQ review[11] examined socioeconomic outcomes among workers with OA in seven studies.[3,221,224,225,260–262] Four studies assessed the change in financial situation after an OA diagnosis and consistently found that workers who had been removed from their job experienced a loss in income. Two studies[224,263] assessed workers' compensation claims and acceptances. In one study,[263] a national workers' compensation board accepted more claims from workers who were removed from the workplace than those who only reduced exposure. A second study[224] concluded that the acceptance rate was similar, regardless of exposure status. Compared to workers who were removed from the workplace, there was a greater increase in medication costs among workers who remained exposed or reduced their exposure.[261]

Overall, the economic consequences of the development of OA are impressive. Among the workers included in the studies, those who left the workplace experienced economic repercussions of reduced income and/or unemployment. Even workers who reduced their exposure or stayed employed at the same workplace appeared to lose some income over time; meanwhile, their medication costs increased.

As with typical asthma, the natural history of WEA can be variable. Patients with asthma are more likely to miss work and to report being less effective when at work, even without workplace exacerbations.[264,265] Studies[260,263,266] investigating socioeconomic outcomes in those patients with WEA have generally shown rates of unemployment and income loss comparable to those with new-onset OA. The economic consequences for these groups should be considered strongly in any management plan.

Compensation

Given the substantial adverse economic and employment consequences of WRA,[3,22] the physician should attempt to obtain as much objective evidence as possible to clarify the diagnosis of WRA, using the approaches discussed above, and in particular while the worker is still employed. Medical and workplace management should be coordinated with the management of compensation. The United States, Canada, and most European countries recognize OA as a compensable disease, and the clinician should support workers compensation claims when appropriate. WEA is less commonly recognized as compensable, although certain compensation systems have started to, such as the one in Ontario, Canada.[67,68,70] Workers' compensation is typically a no-fault compensation system paid for by employers and administered by governmental agencies (in Canada and Europe) or private insurance companies (in the United States).[267] Compensation typically covers related medical expenses, variable income replacement, and some job retraining; however, the systems

vary, with different diagnostic criteria, and variable acceptance of claims and benefits.

Data on compensation systems, such as the extent of benefits, or which compensation strategies may more effectively mitigate the adverse socioeconomic outcomes related to OA, are limited. A substantial number of workers with diagnosed sensitizer-induced OA remain exposed to the causative agent, presumably to avoid unemployment or lesser employment.[221,260,263,268] In one study,[266] workers in whom OA had been diagnosed were more likely to receive compensation benefits than those in whom WEA had been diagnosed. It is difficult to draw conclusions regarding the impact of compensation benefits, as there are other differences between comparison groups in these studies, such as the severity of asthma.

The standard used for workplace causality in most compensation systems is "more probable than not" or > 50% likely to be work related. As noted above, it is in the patient's best interest for the physician to obtain as much objective diagnostic information as possible, both to avoid unemployment in workers who do not have WRA and to be able to assist those who do have WRA to obtain appropriate compensation. Workers should be evaluated for respiratory impairment by the objective assessment of asthma severity using appropriate guidelines, such as that published by the American Thoracic Society.[269] The extent of disability, the ability to work at a specific job, depends on several factors, including the presence of the sensitizing agent, in which case the worker may be completely disabled from workplaces with that specific exposure.

Prevention of WRA

As all WRA is potentially preventable, and given the high incidence of disease worldwide, better prevention efforts are needed.[270,271] In general, prevention may be classified, as follows, as primary, secondary, or tertiary: primary prevention consists of abating hazards before disease or damage has occurred; secondary prevention is aimed at preventing advanced disease by intervening early in the course of the disease (*eg*, at a preclinical or very early stage including removal from exposure); and tertiary prevention provides treatment for advanced disease (*eg*, drug treatment and removal from exposure), which is addressed in detail above in the disease management sections.

Primary Prevention

Irritant-Induced OA and WEA: Irritant-induced OA usually represents a failure of primary preventive measures such that a worker is exposed to an unusually high level of an irritating agent. Primary prevention relies on methods to control exposures (*eg*, isolation/enclosure of the source, improved workplace ventilation, or respirator use). Similar approaches may prevent WEA.

Sensitizer-Induced OA: Primary prevention of sensitizer-induced OA may include substituting a new agent for the causative one in the workplace, isolating or enclosing the process using the causative agent, reducing exposures by improving workplace ventilation or using respiratory personal protective devices (respirators), and educating workers about avoidance maneuvers. By empowering the worker with knowledge, a clinician has the potential to be an effective force for change in workplace exposure control.

Identifying associated risks, such as atopy, among exposed workers was previously proposed as a method of reducing the development of sensitizer-induced OA, but this has limited value. While smoking or atopy are risk factors associated with some causes of sensitizer-induced OA (*eg*, platinum salts and acid anhydrides, or HMW allergens, respectively), the high prevalence of these factors among the general population, compared with the relatively low risk of occupational sensitization, precludes such screening from being a useful strategy. Moreover, this maneuver would exclude many workers in whom OA would never develop and has been discarded as a preplacement strategy; the workplace should be made equally safe for atopic and nonatopic workers.[144] There is no evidence that those workers with preexisting asthma are more likely to become sensitized to work agents than those without asthma, except for the likelihood associated with underlying atopy for some sensitizers. Nevertheless, for workers with preexisting asthma in whom sensitization develops, it may be more difficult to make the diagnosis, especially for LMW sensitizers in which conducting a specific immunologic test may not be feasible to confirm sensitization.

A successful example of intervention by finding a substitute for a common causative agent includes the introduction of nonpowdered NRL gloves into the workplace, which was associated with a reduced incidence of new cases of NRL-related sensitization and OA in a national intervention trial in the German health-care system,[272] and in a large teaching hospital trial.[273] A systematic review[274] found good evidence for the effectiveness of this approach.

An example of reducing exposure to the sensitizer by product modification (*ie*, the encapsulation of asthma-causing detergent enzymes) has been shown to be effective in the detergent industry.[275] The use of ventilation as a main intervention was also effective in an observational study[276] of workers using a

new epoxy resin hardener (tetrachlorophthalic anhydride) in a manufacturing facility. New cases of WRA were reported in 35% of participants. The addition of new workplace ventilation, which reduced dust levels to less than half their preintervention levels, eliminated further new cases of asthma among newly hired workers over a 2-year period.[276]

The introduction of three kinds of respiratory protective devices (mask respirators) [disposable dust-mist respirator, dual-cartridge half-face respirator, and a dual-cartridge powered air purifying full-face respirator] was followed by a reduced annual incidence of OA due to hexahydrophthalic anhydride (a powdery chemical), which is used to make an epoxy resin.[277] Air-supplied respirators (airline respirators) have been recommended[278] to limit exposure to diisocyanates in autobody shops. A later study[279] concluded that negative pressure, air-purifying, half-face respirators equipped with organic vapor cartridges and paint prefilters provide effective protection against diisocyanate exposure in spray and priming operations if workers are properly trained and fitted.

Primary Prevention: Linking Clinical and Public Health Approaches

Some preventive interventions focus on the individual worker, whereas other efforts are directed at groups of workers associated with particular worksites or at the worksite environment itself. Clinicians frequently encounter patients with possible WRA,[280] and have both the opportunity and often an ethical responsibility to facilitate public health-based/population-based interventions in addition to caring for the individual patient. There can be a significant impact by communicating effectively with occupational health professionals (*ie*, clinicians and others).

Physicians are frequently in leadership positions in their own health-care industry facilities, which can have substantial exposures to cleaning agents, latex, and other factors linked to WRA, and they can institute changes more easily there than in factory settings. For example, many physicians have contributed to policies limiting unnecessary exposures to latex. Astute clinicians can discover heretofore unrecognized causes of sensitizer-induced OA by recognizing the temporal pattern associating symptoms or spirometry changes with work.

In the course of clinical practice, clinicians may uncover worksites and industries where cases of WRA occur due to known causative agents. The submission of appropriate reports to public health surveillance and regulatory systems can link clinical and public health approaches. Several voluntary reporting programs have been established in the United States (Sentinel Event Notification System for Occupational Risks [or SENSOR][21,105]), the United Kingdom (Surveillance of Work-Related & Occupational Respiratory Disease [or SWORD][281,282]), and South Africa (Surveillance of Work-related and Occupational Respiratory Diseases in South Africa [or SORDSA][283]). Reports of suspected WRA may then encourage exposure control interventions.

The development of WRA should be considered to be an occupational sentinel health event; to serve as a warning signal that material substitution, control of exposure, protective equipment, or medical care may be required; or that other workers may also be exposed.[62] In addition, several categories of occupational characteristics indicate the need to consider that a risk of WRA exists in the workplace (Tables 2–5). As examples, asthmatic workers in industrial settings with exposure to dusts, fumes, and sprays would be expected to have an increased risk of WEA, and those in domestic or industrial cleaning jobs would be subject to an increased risk of WEA related to common allergens and cleaning products. Workers in bakeries or companies using diisocyanates would be expected to have an increased risk of OA compared with clerical workers.

In the United States, the National Institute for Occupational Safety and Health (NIOSH), which is not a regulatory agency, may conduct thorough worksite evaluations, which are known as Health Hazard Evaluations (HHEs), in selected situations if requested by a worker or employer. Such HHEs include an objective assessment of exposures and the workers as well as recommendations for the specific worksite. In addition, HHEs often lead to information that may benefit other worksites with similar hazards.

Clinicians should also advise patients with suspected sensitizer-induced OA about requesting the employer (*eg*, through a workplace health and safety committee or union) or the workers compensation insurer to take actions that may reduce impairment in other cases and prevent cases (*eg*, by screening programs and improved exposure control). If the physician has the permission of the patient, the employer may be contacted/advised regarding appropriate actions.

Panel Consensus

11. For workers who are potentially exposed to sensitizers or uncontrolled levels of irritants, the panel advises primary prevention through the control of exposures (*eg*, elimination, substitution, process modification, respirator use, and engineering control).

Secondary Prevention

While primary prevention may markedly reduce the incidence of some causes of sensitizer-induced OA, the ongoing high prevalence and incidence of the disease indicates the need for secondary prevention also. Medical (or health) surveillance has been defined as the serial performance of an observation or test that is used to detect evidence of a disease process that can be altered by appropriate intervention; it is a method of secondary prevention.[284] In the context of sensitizer-induced OA, the purpose of a medical surveillance program is to detect in workers the indicators of early sensitization or sensitizer-induced OA early in its course before there is progression to permanent asthma, in addition to providing the potential to link with appropriate interventions to prevent further cases of sensitizer-induced OA. This does not apply to irritant-induced asthma, because the disease process starts with one or more high irritant exposures.

Rationale for Medical Surveillance

Medical surveillance programs have been recommended by various authors, as well as in governmental guidelines and regulations. The main rationale for medical surveillance, however, is the considerable indirect evidence that once sensitizer-induced OA has developed in a worker, the outcome is best with early diagnosis, early removal from exposure to the causative agent, and milder asthma at the time of removal from exposure.[79,221,223,229,285] In addition, screening programs may provide a means to measure the impact of primary prevention efforts.[286] However, until the past few years there has been little or no direct evidence demonstrating that groups undergoing medical surveillance actually have better outcomes compared with groups not subjected to this maneuver.

Medical surveillance programs for sensitizer-induced OA typically include a symptom questionnaire, spirometry, and a serologic test or SPT (for numerous HMW allergens and occasional LMW allergens, for which one can detect specific IgE antibodies). An SPT is more sensitive than an *in vitro* IgE antibody test in identifying workers with allergic sensitization to HMW proteins and OA, and is preferable for screening exposed workers.[133,134,287] One can examine evidence from past programs according to whether immunologic tests are or are not available (diisocyanates have been most studied for the latter category). However, past studies must be interpreted with the caveat that medical surveillance may have been established in conjunction with other measures such as exposure control (*ie*, primary prevention), whether by legislation or voluntary, so that the attribution of benefit is not necessarily clear. Furthermore, it is often difficult to determine which component of the surveillance program is effective.

Surveillance With Immunologic Tests Available

SPTs in the detergent enzyme industry have been feasible and successful[144,275,286,288] in combination with exposure controls[288] and process changes (*ie*, granulated enzymes rather than powder enzymes). In some jurisdictions,[288] the exclusion of atopic persons from work had been incorporated in past decades as part of the control program. Subsequent monitoring revealed that the percentage of SPT-positive conversions fell steadily. Another medical surveillance program[144] for workers with enzymes included filling out periodic questionnaires, spirometry, and SPTs every 6 months for 2 years (when the incidence of sensitization is highest) and then yearly after that time. The control of exposure (primary prevention) occurred concurrently. The rates of asthma (and sensitization) declined significantly in temporal association with this surveillance and other[286] programs. In the 1990s, an outbreak of enzyme-induced, sensitizer-induced OA occurred at a modern detergent factory using several kinds of encapsulated enzymes,[289] despite encapsulation, perhaps because of the rapid introduction of new enzyme types, the failure to keep exposure within industry guidelines, and the absence of health surveillance.

Among workers who were exposed to complex platinum salts, a positive SPT result was highly predictive of the development of sensitizer-induced OA if exposure was continued; work-related symptoms may develop in 100% of patients with a positive SPT result.[290] A medical surveillance program of these workers in Germany (symptom questionnaires and SPTs were administered biannually for the first year, then annually)[291] identified work-related symptoms, which resolved in most workers during follow-up after their removal from exposure, in 64% of SPT converters. However, direct evidence of a reduction in the development of OA was difficult to document because of a lack of a concurrent "control" group without surveillance measures, and lack of information on changes in industrial hygiene measures and workplace exposures during the program. A report from South Africa (Report No. 24/86; Johannesburg, South Africa: National Centre for Occupational Health) that was cited in a review article[292] described workers with positive test results who continued to be exposed until they declared symptoms. Approximately 10% of those in whom asthma developed and had been removed from exposure continued to have asthma when seen by a physician 1 to 2 years later. In

a US facility in the absence of surveillance, among those in whom asthma developed and had stopped work for a mean time of 5 years, 48% remained symptomatic.[293] Thus, surveillance and removal of workers who are sensitized appears to result in better outcomes than no surveillance or surveillance with delayed removal from exposure.

Surveillance in the Absence of Immunologic Tests

Medical surveillance programs for diisocyanates to date have relied on symptom questionnaires and spirometry, but not immunologic tests. A retrospective evaluation[294] of a diisocyanate program in Canada has suggested a benefit from the program or some component of it. Compared with OA due to other causes, the annual number of claims for OA due to diisocyanate exposure initially rose and then declined, suggesting that case finding explained this temporal trend. This was supported by the finding that those workers with OA due to diisocyanate exposure had experienced a shorter symptom duration before diagnosis, had milder asthma, and were less likely to have been hospitalized.[294] In addition, companies using diisocyanates that were known to be in compliance with the program showed an earlier diagnosis of OA (mean time to diagnosis, 1.7 years) compared with those companies that were not known to be in compliance (mean time to diagnosis, 2.7 years) and a trend toward better outcome.[79]

Limited data are available to identify whether the administration of questionnaires or spirometry testing is the beneficial component of medical surveillance.[289,295] Questionnaires (*ie*, medical history) have been thought to be sensitive but not specific[59]; however, earlier studies[296,297] found low sensitivity (missed cases of asthma in the absence of reported symptoms; "potential problem of . . . misleading responses"). With respect to the frequency of monitoring, data do not exist to advise a "best" or "most efficient" frequency for surveillance. Testing conducted every 6 months probably provides as good an outcome as does testing every 3 months and is practicable.[292] A cost-effectiveness (CE) analysis of surveillance for diisocyanate asthma[298] using parameters for inclusion obtained from the literature and an expert panel (including time to diagnosis with and without surveillance)[79] found a favorable CE ratio that supports surveillance for diisocyanate asthma. The simulation model, which was based on yearly OA surveillance, revealed that surveillance resulted in a benefit over a passive case finding for 100,000 exposed workers over 10 years of 683 fewer disabled workers, 3.3 million more symptom-free days, and 1,831 additional quality-adjusted life-years at an additional cost of $44 million. This analysis estimated that surveillance was cost saving from the societal perspective, but not from the employer perspective, which estimated an incremental CE of $24,000 per quality-adjusted life-year ($13.33 per symptom-free day; $64,000 per case of disability prevented). Although such findings compare favorably with commonly recommended surveillance tools, the large difference in CE comparing societal and employer perspectives supports the argument[299] that mandatory regulation may be the most effective way to implement surveillance for certain occupational diseases.

Panel Consensus

12. An individual diagnosis of OA represents a potential sentinel health event:
    - Evaluate the workplace to identify and prevent other cases of OA in the same setting.
    - For work environments with potential exposure to sensitizers, the Consensus Panel advises secondary preventive measures, including medical surveillance using tools such as questionnaires, spirometry, and, where available, immunologic tests.

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Errata

In the June 2008 supplement, in the article by Hirsh et al, "Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]:71S–109S), on page 99S, in column one, Recommendation 2.5.2, the text should read "For patients with acute ST-segment elevation myocardial infarction receiving fibronolytic therapy who have preserved renal function (< 2.5 mg/dL [220 μmol/L] in males and < 2.0 mg/dL [175 μmol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A)." The online version has been corrected, and that version should be used.

In the June 2008 supplement, in the article by Goodman et al, "Acute ST-Segment Elevation Myocardial Infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]:708S–775S), on page 710S, in column one, Recommendation 2.5.2 (and on page 739S column one), the text should read "For patients with acute ST-segment elevation myocardial infarction receiving fibronolytic therapy who have preserved renal function (< 2.5 mg/dL [220 μmol/L] in males and < 2.0 mg/dL [175 μmol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A)." The online version has been corrected and that version should be used.

In the June 2008 supplement, in the article by Kearon et al, "Antithrombotic Therapy for Venous Thromboemobolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]: 454S–545S), the conflict of interest disclosures from the authors were inadvertently left out. They are as follows: Dr. Kearon discloses that he has received grant monies from the Canadian Institutes for Health Research and the Heart and Stroke Foundation of Canada. He is also on an advisory committee for GlaxoSmithKline and Boehringer Ingelheim. Dr. Agnelli reveals no real or potential conflicts of interest or commitment. Dr. Goldhaber discloses that he has received grant monies from Mitsubishi, Boehringer Ingelheim, Sanofi-Aventis, Eisai, GlaxoSmithKline, and AstraZeneca. He has also received consultant fees from Sanofi-Aventis, Eisai, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr. Raskob discloses that he has served on the speaker bureau and advisory committees and has received consultant fees from Bayer, BMS, Daiichi-Sankyo, Pfizer, Sanofi-Aventis, Takedo and Boehringer Ingelheim. Dr. Comerotta discloses that he is on the speaker bureaus of Sanofi-Aventis, Bristol-Myers Squibb, and GlaxoSmithKline and serves on an advisory committee for ConvaTec, and Bacchus Vascular. He is also a shareholder of LeMaitre Vascular.

In the September 2008 supplement by Tarlo et al, "Diagnosis and Management of Work-Related Asthma: American College of Chest Physicians Consensus Statement" (Chest 2008; 134:1S–41S), some of the subheadings are misleading in the print version. The online version has been corrected and should be used. There is no change to the text, but the level of headings shown on pages 7S–9S, 17S, and 31S–32S is more clear in the corrected online edition. Also, on the Table of Contents pages the Endorsements should read "The Canadian Society of Allergy and Clinical Immunology and The Canadian Thoracic Society".

In the July 2008 issue, in the correspondence by BaHammam et al, "Positive Airway Pressure Therapy and Daytime Hypercapnia in Patients With Sleep-Disordered Breathing" (Chest 2008; 134:218–219), the first author's surname was misspelled. It is BaHammam. It has been corrected in the online edition.

Correction

I have come to realize that I neglected to provide as full a potential conflict of interest statement as I could have in my review article, "Update on the Management of COPD" (Chest 2008; 133:1451–1462). I wish to disclose the following: Bartolome R. Celli has been reimbursed by GSK, BI, Pfizer, AZ, Almirall, and Esteve for participating in advisory boards and spoken at different meetings. The division that Dr. Celli heads has been awarded research grants for different medication trials by the same companies and for the discovery of new biomarkers in COPD, and has received grants for the participation in the development of biological lung volume reduction surgery from the company AERIS. Bartolome R. Celli, MD, FCCP, Pulmonary and Critical Care Medicine, Caritas St. Elizabeth's Medical Center, Boston, MA.