Assessment and Management of Occupational Asthma

Paul Cullinan, MD[a], Olivier Vandenplas, MD, PhD[b], and David Bernstein, MD[c] *London, United Kingdom; Yvoir, Belgium; and Cincinnati, Ohio*

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Learning objectives:

1. To recognize the range of diagnostic tests useful in the stepwise assessment of a worker with possible occupational asthma.

2. To identify important causes of sensitizer-induced occupational asthma.

3. To explain the principles behind the successful management of a patient with occupational asthma.

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Exposures at work can give rise to different phenotypes of "work-related asthma." The focus of this review is on the diagnosis and management of sensitizer-induced occupational asthma (OA) caused by either a high- or low-molecular-weight agent encountered in the workplace. The diagnosis of OA remains a challenge for the clinician because there is no simple test with a sufficiently high level of accuracy. Instead, the diagnostic process combines different procedures in a stepwise manner. These procedures include a detailed clinical history, immunologic testing, measurement of lung function parameters and airway inflammatory markers, as well as various methods that relate changes in these functional and inflammatory indices to workplace exposure. Their diagnostic performances, alone and in combination, are critically reviewed and summarized into evidence-based key messages. A working diagnostic algorithm is proposed that can be adapted to the suspected agent, purpose of diagnosis, and available resources. Current information on the management options of OA is summarized to provide pragmatic guidance to clinicians who have to advise their patients with OA. © **2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:3264-75)**

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[a]Department of Occupational and Environmental Medicine, Royal Brompton Hospital and Imperial College (NHLI), London, United Kingdom
[b]Department of Chest Medicine, Centre Hospitalier Universitaire UCL Namur, Université Catholique de Louvain, Yvoir, Belgium
[c]Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, Ohio

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Corresponding author: Olivier Vandenplas, MD, PhD, Department of Chest Medicine, Centre Hospitalier Universitaire UCL Namur, Université Catholique de Louvain, 1 Avenue G. Therasse, Yvoir B-5530, Belgium. E-mail: olivier.vandenplas@uclouvain.be.

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Abbreviations used
FENO- Fractional exhaled nitric oxide
HMW- High molecular weight
IIA- Irritant-induced asthma
LMW- Low molecular weight
NPV- Negative predictive value
NSBH- Nonspecific bronchial hyperresponsiveness
OA- Occupational asthma
PEF- Peak expiratory flow
PPV- Positive predictive value
SIC- Specific inhalation challenge
sIgE- Specific IgE
SPT- Skin prick test

INTRODUCTION

Workplace exposures can lead to the development of different phenotypes of "work-related asthma"[1] encompassing both asthma caused by work, referred to as occupational asthma (OA), and preexisting or coincident asthma exacerbated by nonspecific stimuli at work, commonly referred to as work-exacerbated asthma[2] (Figure 1).

OA can be broadly defined as "a disease characterized by airway inflammation, variable airflow limitation, and airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace,"[3] whereas the definition issued by the American College of Chest Physicians further stipulates that "Occupational asthma 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, which is termed sensitizer-induced OA (OA), or by exposure to an inhaled irritant at work, which is termed irritant-induced OA (IIA)."[4]

Sensitizer-induced OA is characterized by a "latency period" of asymptomatic exposure before the onset of work-related asthma symptoms reflecting the development of immunologic sensitization. The agents causing OA are usually categorized into high-molecular-weight (HMW) (glyco)proteins from vegetal or animal origin and low-molecular-weight (LMW) agents (<1 kDa), which include reactive chemicals, metals, and wood dusts (Table I). Although more than 400 substances encountered at work have been documented as causing sensitizer-induced OA[5-7] (www.asthme.cssst.qc.ca; www.occupationalasthma.com), flour and isocyanates remain the most frequent causes of OA in industrialized countries, accounting for about half of the reported cases in the last decade.[8] Nevertheless, the distribution of causal agents may vary widely across geographical areas, depending on the pattern of industrial activities. HMW proteins and a few LMW compounds (eg, platinum salts, reactive dyes, acid anhydrides, sulfonechloramide, and some wood species) act through a demonstrable type I IgE-associated hypersensitivity mechanism, but for most LMW agents, the immunologic mechanisms leading to airway sensitization remain poorly elucidated.[9] Although asthmatic reactions induced by both HMW and LMW agents are characterized by a predominant eosinophilic airway inflammation,[10] there are differences in the clinical characteristics of OA caused by these 2 broad categories of causal agents.[8] OA caused by HMW agents is more frequently associated with work-related rhinitis/conjunctivitis, atopy, and early asthmatic reactions on exposure to the causal agent, whereas OA due to LMW agents is associated with a higher prevalence of daily sputum production and late asthmatic reactions.[8] Interestingly, asthmatic reactions caused by HMW agents elicit a greater postchallenge increase in fractional exhaled nitric oxide (FENO) compared with those caused by LMW agents, further supporting differences in underlying pathobiologic pathways.[8,11] Nevertheless, a recent study challenged the traditional concept of pooling various LMW agents into a single category, presuming implicitly that they share similar pathophysiologic mechanisms.[12] This study found that acrylate-induced OA has phenotypic characteristics (ie, concomitant work-related rhinitis and greater exposure-related increases in FENO) similar to those described in IgE-mediated OA due to HMW agents, suggesting that acrylates may induce OA through different immunologic mechanisms compared with other LMW agents.

The term IIA historically refers to asthma caused by short-term high-level exposures to irritant substances encountered at work, the best documented form being the reactive airways dysfunction syndrome.[13-15] It is now widely acknowledged that various clinical phenotypes can be distinguished within the spectrum of IIA: (1) acute-onset IIA (ie, reactive airways dysfunction syndrome), which is characterized by the rapid onset of asthma within hours of a single exposure to a very high level of irritant substances; (2) asthma that develops in workers with a history of repeated symptomatic high-level exposures to irritants; and (3) asthma occurring with a delayed onset after chronic exposure to moderate levels of irritants.[15]

DIAGNOSTIC ASSESSMENT

Establishing or excluding a diagnosis of OA requires a high level of accuracy because the condition has not only significant health consequences for affected workers but also substantial socioeconomic impacts for them, their employers, and society.[4,16-19] Missing a diagnosis of OA may lead to continued exposure and progressive worsening of asthma; conversely, diagnosing OA when it is not present may lead to inappropriate removal from exposure and unnecessary financial and social consequences. Work-related asthma symptoms are frequently (~20%) reported by adults with asthma,[2] but about half of them fail to show objective evidence of asthma worsening when they are exposed to their workplace or to the suspected agents under laboratory conditions.[20,21] Furthermore, a substantial proportion of subjects evaluated for work-related asthma-like symptoms fail to demonstrate any functional evidence of asthma.[22]

Diagnosing OA still remains a challenge for the clinician because there is no simple test with a sufficiently high level of accuracy. Instead, the diagnostic process combines different procedures in a stepwise manner.[4,16,18,23] These include a clinical history, assessment of nonspecific bronchial hyperresponsiveness (NSBH), immunologic testing if available, serial assessments of functional and inflammatory changes related to workplace exposure, and specific inhalation challenge (SIC) with the suspected occupational agent(s) in the laboratory. The available information on the validity and feasibility of these procedures is critically reviewed herein to provide pragmatic guidance to clinicians who are investigating work-related asthma symptoms.

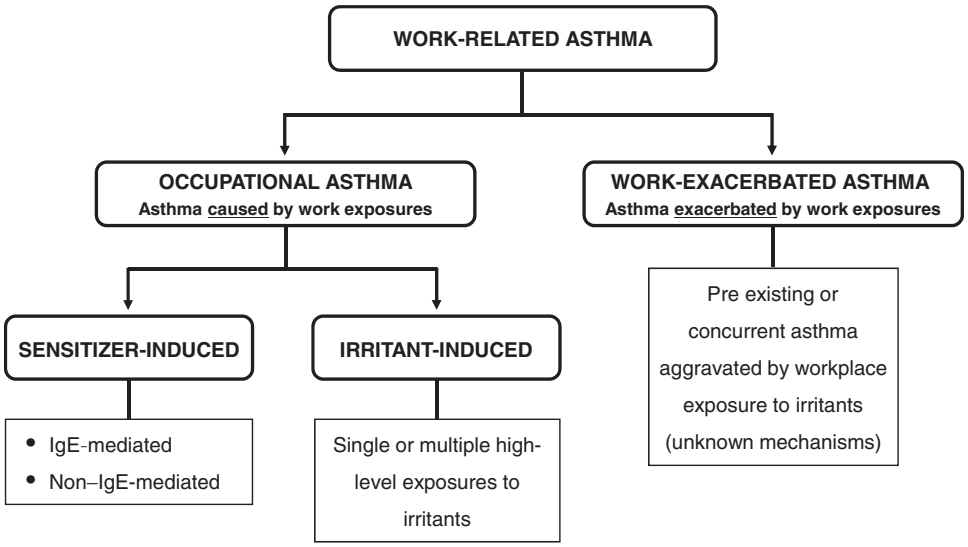

FIGURE 1. Classification of work-related asthma phenotypes.

Baseline assessment

Clinical and occupational history. The possibility of work-related asthma should be considered in every adult patient with new-onset asthma. The most relevant items in the clinical history include (1) occupation (description of tasks and processes and identification of direct and indirect exposures to potential workplace asthmagens); (2) respiratory symptoms (nature, latency period, temporal relationship with work); and (3) associated comorbid work-related disorders (rhinitis/conjunctivitis, urticaria, contact dermatitis).[21,24]

Typically, affected workers initially experience asthma symptoms during the work shift, with remission or improvement during weekends and holidays. However, this pattern is frequently obscured by late asthmatic reactions occurring after the work shift and by asthma symptoms triggered by nonspecific stimuli outside the workplace. In addition, as the disease progresses, remission of symptoms in the evening or during weekend tends to fade, and longer periods off work are necessary for improvement.

Although a thorough clinical and occupational history is key to the diagnostic approach, the diagnosis of OA cannot be made solely on the basis of a compatible history or exposure. Available data clearly indicate that clinical history has a high sensitivity (~90%) but a very low specificity (27%-50%) for diagnosing OA.[20,21,25,26] Very few items included in a clinical questionnaire are satisfactory predictors of the presence of OA. Among these, wheezing and rhinoconjunctivitis symptoms at work are associated with the highest specificity, especially when HMW agents are involved.[21,27] An 11-item self-administered questionnaire with the addition of age and exposure duration correctly classified 80% of workers referred for probable OA to a tertiary center.[27]

Assessment of NSBH. After the clinical history, the next step is the documentation of asthma through the demonstration of reversible airflow obstruction or NSBH to pharmacological agents in subjects without airflow limitation.[4] But NSBH has a low specificity (36%-64%) and accordingly a low positive predictive value (PPV) for diagnosing OA (55%-63%).[28-30] However, the presence of NSBH showed sensitivities ranging from 84% to 87% and negative predictive values (NPVs) ranging from 69% to 86% in predicting the result of an SIC.[28-30] Notably, a retrospective study of a large cohort of subjects investigated through SIC demonstrated that the absence of NSBH (ie, concentration of methacholine/histamine causing a 20% fall in FEV_1 [PC_{20}] >16 mg/mL) in subjects recently exposed to the suspected agent makes the diagnosis of OA highly unlikely.[29] The sensitivity of NSBH increased from 67% when the subjects were away from work at the time of assessment to 98% when NSBH had been measured at least once when they were still at work[29]; the corresponding NPVs were 82% and 98% when NSBH was measured while subjects were exposed at work. Nevertheless, there have been reports of normal NSBH both before and after a positive SIC in 6% to 10% of subjects with OA.[29,30]

Markers of airway inflammation. There is increasing interest in the noninvasive assessment of airway inflammation through sputum cell analysis and measurement of FENO levels as complementary tools to lung function tests in the diagnosis of asthma[31,32] and OA.[33] Sputum induction and processing are time-consuming, require technical expertise, and are unsuccessful in a substantial fraction (20%-30%) of subjects.[34] In contrast, the measurement of FENO levels as a surrogate marker for eosinophilic airway inflammation is simple, fast, and feasible in almost all patients.[32] However, there is an important degree of discordance between NSBH, sputum eosinophilia, and FENO level, indicating that these indices reflect different dimensions of asthma.[32,35-38]

There is scarce information on the usefulness of a single assessment of FENO or sputum eosinophils in diagnosing OA. Overall, an increased FENO level (≥25 ppb) and sputum eosinophil count (≥3%) alone showed lower sensitivity rates (FENO, 47%-60%; sputum eosinophils, 29%) than the measurement of NSBH, whereas the specificity rates (FENO, 71%-78%; sputum eosinophils, 78%-86%) were higher (Table II).[30,39,40] The PPVs

TABLE I. Principal agents causing sensitizer-induced OA

Source/chemical class	Agent	Workers/occupations at risk
HMW agents		
Animals	Laboratory animals (mice, rats)	Research laboratory workers
	Cows	Farmers
	Seafood (fish, crustaceans, and molluscs)	Seafood processors, fishermen, aquaculturists
	Insects (eg, flies, locusts, worms, spiders, predatory mites/bugs, parasitoidal wasps, and nematodes)	Laboratory workers, fish food producers, fruit growers, biological pest control in greenhouses
	Animal-derived products:	Food processors, bakers
	• Milk/egg proteins, bovine serum albumin	Natural dye producers
	• Carmine from *Dactolylopius coccus*	
Plants	Flour (wheat, rye, barley, buckwheat)	Bakers, pastry/pizza makers, millers
	Latex (natural rubber latex from Hevea tree, *Ficus benjamina*)	Health care workers, laboratory technicians, floral workers
	Spices (eg, aniseed, cinnamon, coriander, fennel, and nutmeg)	Food industry
	Beans, seeds (eg, coffee, soybean, linseed, and lupine)	Food processors
	Roots, leaves (tea, chamomile, and henna)	Tea and herbal tea processors, hairdressers
	Ornamental plants	Horticulture
	Pollen (tomato, bell pepper, broccoli, and saffron)	Greenhouse workers
	Gums (acacia, guar, tragacanth, and psyllium)	Food industry, carpet manufacturing, pharmaceutical and health care workers
	Plant-derived products: colophony	Electronic soldering
Enzymes from various origins	α-Amylase, maxatase, alcalase, cellulase, papain, bromelain, pancreatin	Baking product production, bakers, detergent production, pharmaceutical industry, food industry
Molds	Various species	Biotechnology plants, waste management, wood workers, greenhouse workers, food industry
LMW agents		
Isocyanates	Toluene diisocyanate, methylene diphenyl-diisocyanate, hexamethylene diisocyanate	Polyurethane production, plastic industry, insulation, molding, spray painting
Acid anhydrides	Phthalic, trimellitic, maleic, tetrachlorophthalic anhydrides	Epoxy resin workers
Acrylates	Cyanoacrylates, methacrylates, plain acrylates	Adhesives, printing inks, paints and coatings, dental care, beauty care
Amines	Polyamine epoxy resin hardeners	Construction coatings, adhesives, plastic composites manufacturing, pipe relining
Biocides	Formaldehyde, glutaraldehyde, quaternary ammonium compounds, chlorhexidine, triclosan	Health care workers, cleaners
Drugs	Penicillin derivatives, cephalosporins, clarithromycin, minoxidil, ferrimanitol ovalbumin, glucosamine	Pharmaceutical workers, health care workers
Persulfate salts	Hair bleach	Hairdressers
Reactive and other dyes	Reactive black 5, pyrazolone derivatives, vinyl sulphones	Textile workers, food industry workers
Metals	Platinum salts, chromium, nickel, cobalt	Metal refinery, metal alloy production, electroplating, welding
Metal working fluids	Uncertain causal agent(s): biocides (eg, isothiazolinone derivatives, and bismorpholine), microorganisms, metals	Metal cutting
Woods	Red cedar, iroko, obeche, oak, and others	Sawmill workers, carpenters, cabinet and furniture makers

ranged from 67% to 84% for FENO and from 41% to 64% for sputum eosinophils, whereas the NPVs were 50% to 52% and 45% to 82%, respectively. So far, only 1 study compared the diagnostic usefulness of a single assessment of NSBH, FENO, and sputum eosinophils in the same population.[30] A substantial proportion (59%) of subjects with OA ascertained by a positive SIC who failed to demonstrate baseline NSBH showed either a FENO level of 25 ppb or higher or a sputum eosinophil count of

TABLE II. Combining diagnostic tests at baseline assessment

Procedures	Prevalence of OA*	Sensitivity (%)	Specificity (%)	Reference
NSBH alone (latex)	19 of 29 (66%)	90	10	Quirce et al[26]
NSBH + SPT (latex)		84	70	
NSBH alone (HMW agents)	NA	79 (68-88)†	51 (35-67)†	Beach et al[28]
NSBH + SPT (HMW agents)		61 (21-90)†	82 (54-95)†	
NSBH + sIgE (HMW agents)		36 (1-96)†	85 (48-97)†	
Baseline NSBH alone (various agents)	133 of 240 (55%)	87	36	Beretta et al[30]
FENO ≥25 ppb		47	71	
FENO ≥50 ppb		20	94	
NSBH + FENO ≥25 ppb		44	78	
NSBH + FENO ≥50 ppb		20	94	
NSBH or FENO ≥25 ppb		91	29	
NSBH or FENO ≥50 ppb		88	36	
Sputum eosinophils ≥1%	79 of 138 (57%)	72	46	
Sputum eosinophils ≥2%		39	68	
NSBH + sputum eosinophils ≥1%		63	63	
NSBH + sputum eosinophils ≥2%		33	76	
NSBH + sputum eosinophils ≥3%		27	81	
NSBH or sputum eosinophils ≥1%		94	17	
NSBH or sputum eosinophils ≥2%		91	25	

NA, Not available.
*SIC used as confirmatory test for OA.
†95% CI within parentheses.

1% or higher. Although FENO level and sputum eosinophil count alone were less sensitive than the measurement of NSBH, combining either the presence of NSBH or a FENO level of 25 ppb or higher or a sputum eosinophil count of 1% or higher increased the sensitivity for identifying OA from 87% (95% CI, 80%-92%) for NSBH alone to 91% (95% CI, 85%-95%) and 94% (95% CI, 86%-98%), respectively. These sensitivity rates are similar to those of NSBH measurement in subjects still exposed at work. It follows that a normal FENO level and/or sputum eosinophil count make the diagnosis of OA highly unlikely in subjects removed from exposure who fail to demonstrate NSBH. Alternatively, a high FENO level and/or sputum eosinophil count could be helpful in identifying formerly exposed patients who may have OA despite the absence of NSBH and who should complete further investigation before excluding the diagnosis.

Immunologic testing. Skin prick tests (SPTs) and assessment of serum specific IgE (sIgE) antibodies are useful to demonstrate IgE-mediated sensitization to most HMW and some LMW occupational agents. However, their contribution is limited by the lack of standardized and validated extracts or reagents for many occupational agents.[41] The allergenic potency of SPT extracts from some HMW occupational agents varies significantly among manufacturers.[42,43] In addition, available validation studies of immunologic tests were performed using different *in vitro* assays and most often with "in-house" reagents.[44] SPT with LMW agents will not be considered here because most of these agents are potentially irritant to the skin and may produce false-positive results.[45]

In a systematic review of studies published till 2004,[28] the pooled sensitivity of SPT for HMW agents was 81% (95% CI, 70%-88%) in comparison with SIC, whereas the pooled specificity was low (60% [95% CI, 42%-75%]). For sIgE against HMW agents, the sensitivity was 73% (95% CI, 64%-81%), whereas the specificity was higher than that provided by SPTs (79% [95% CI, 51%-93%]). A more recent meta-analysis of studies published between 1967 and 2016[44] provided concordant estimates for the assessment of serum sIgE: a pooled sensitivity of 74% (95% CI, 66%-80%) and a specificity of 71% (95% CI, 63%-77%) for HMW allergens. Accordingly, immunologic tests may clearly establish IgE-mediated sensitization but, alone, do not confirm or exclude a diagnosis of OA in workers exposed to HMW agents with an appropriate level of confidence. However, for some HMW agents increasing the cutoff value for a positive sIgE test result (ie, ≥2.22 kU_A/L for wheat flour, ≥9.64 kU_A/L for rye flour, and ≥4.41 kU_A/L for natural rubber latex) increases both the specificity and PPV to more than 95%.[46,47] Component-resolved analysis of sIgE against recombinant allergens of wheat[48] and natural rubber latex[47] improved only marginally the diagnostic efficiency of high levels of sIgE against the whole allergen extracts.

Both meta-analyses found pooled sensitivity estimates for sIgE against LMW agents (31% [95% CI, 23%-41%][28] and 28% [95% CI, 18%-40%][44]) that were much lower than those against HMW agents, but with a higher specificity (89% [95% CI, 85%-92%][28] and 89% [95% CI, 77%-95%]).[44] These data indicate that the presence of sIgE against LMW agents when available, such as isocyanates or acid anhydrides, is associated with a high likelihood of a positive SIC result, but a very low sensitivity and poor performance for ruling out a diagnosis of OA.

More importantly in the context of a stepwise diagnostic approach, available data indicate that combining a positive SPT or sIgE test result with the presence of NSBH increases the specificity and PPV of each test alone (Table II).[26,28] Therefore, a positive SPT or sIgE test result to either HMW or LMW agents may be regarded as an alternative to SIC in

TABLE III. Advantages and limitations of the procedures used for investigating the effect of workplace exposure

Procedure	Advantages	Limitations
Serial assessments of PEF	• Does not require expensive equipment and can be used in any health care setting	• Impossible to perform when the worker has already been definitively removed from exposure
	• Assessment during usual work exposure	• Recording at and away from work may be difficult to arrange and may imply indirect costs
	• Possible fabrication of results can be prevented by data-logging instruments	• Not suitable in subjects with a history of severe work-related reactions
	• Computer-based analysis of PEF recordings overcomes within- and between-observer variability	• Requires careful instruction and training of subjects because measurements are effort-dependent
	• Especially useful when (1) the subject is exposed to multiple asthmagens at work; (2) no asthmagen has been identified at work; (3) facility for performing SIC is not easily available; and (4) the conditions of exposure at work cannot be reproduced in the laboratory	• Requires subjects' collaboration for measurements during prolonged periods: acceptable and interpretable recordings obtained in only ~60% of subjects
		• No precise identification of the causal agent
		• Moderate sensitivity (82% [95% CI, 76%-90%]) but a high specificity (88% [95% CI, 80%-95%]) as compared with SIC
Serial assessments of NSBH	• May provide additional evidence to the diagnosis of OA	• Time-consuming
		• Provides only slight improvement in sensitivity over PEF recordings alone, but a decrease in specificity
Serial assessments of sputum eosinophils	• Impossible to falsify	• Expensive and time-consuming
	• An increase in sputum eosinophils at work enhances the specificity of PEF analysis	• Requires standardized methodology and qualified technologists
		• Not widely available
		• Substantial (~25%) proportion of subjects fail to produce suitable sputum samples
		• Does not by itself allow for confirming or excluding a diagnosis of OA
Serial assessments of F_{ENO}	• Noninvasive	• Lack of validation
	• Fast and easy to perform	• Difficult to interpret
		• Affected by confounding factors (eg, smoking and inhaled corticosteroids)

TABLE IV. Combining changes in functional and inflammatory indices on exposure to occupational agents

Procedure	Prevalence of OA*	Sensitivity (%)	Specificity (%)	Reference
Serial PEF alone (red cedar)	14 of 23 (61%)	86	89	Côté et al[52]
Serial PEF + change in NSBH at/off work†		92	62	
Serial PEF alone (various agents)	25 of 61 (41%)	81	74	Perrin et al[53]
Serial PEF + change in NSBH at/off work†		84	61	
Serial PEF alone (various agents)	23 of 45 (51%)	63-87	48-62	Girard et al[54]
Serial PEF + change in NSBH at/off work†		60-88	37-62	
Serial PEF + increase in sputum eosinophils >1% at work		50	75	
Serial PEF + increase in sputum eosinophils >2% at work		36	80	
Change in NSBH† pre-/post-SIC	229 of 618 (37%)	52	85	Racine et al[55]
Increase in sputum eosinophils >3% pre-/post-SIC		57	90	
Change in NSBH† + increase in sputum eosinophils >3% pre-/post-SIC		24	97	
Change in NSBH† or increase in sputum eosinophils >3% pre-/post-SIC		84	74	

*SIC used as confirmatory test for OA.
†Change in NSBH means a 2- or 3-fold decrease in the concentration of methacholine causing a 20% fall in FEV_1.

establishing a diagnosis of probable OA in subjects with documented NSBH.[28] Predictive models that incorporate both clinical characteristics and objective tests (ie, the results of NSBH assessment and SPT to the suspected occupational agent) have been recently developed for identifying OA induced by HMW agents.[49] These models showed that adding the presence of certain clinical characteristics (ie, age <40 years, work-related conjunctivitis, and inhaled corticosteroid use) increases the specificity to more than 95% and the PPV to more than 90% for predicting a positive SIC result and provides a higher discriminative ability for diagnosing OA compared with the combination of positive NSBH test result and SPT without the clinical characteristics. However, these predictive models have been validated only in those subjects who were exposed at work within the last month before evaluation. For practical use, the authors transformed these models into clinical scores, which can be easily computed using a calculator available at https://qxmd.com.

Assessment of functional and inflammatory changes related to workplace agents

The advantages and limitations of the procedures used for investigating the effect of workplace exposure to occupational agents on functional and inflammatory outcomes are summarized in Table III.

Serial measurements of peak expiratory flow/ FEV_1. The few available data indicate that cross-shift changes in FEV_1 and peak expiratory flow (PEF) show a low sensitivity for identifying OA (50%-60%),[50,51] but may have a high specificity (91%).[51]

Serial PEF recording during periods at and off work is a simple and inexpensive tool to investigate objectively the relationship between workplace exposure and changes in airway caliber (Table IV).[16] At least 4 PEF readings per day are required, at and away from work, for a period of at least 3 weeks to obtain reliable records. Measured values should be plotted as daily minimum, mean, and maximum values, together with daily PEF variability calculated as the difference between the highest and the lowest PEF expressed as a percentage of either the mean or the highest value. The upper limit of normal for intraday variability in PEF measurements is approximately 20%. The major limitation of serial PEF measurements results from the lack of a standardized method for interpreting the results. The work-relatedness of PEF values can be evaluated through the visual inspection by experienced physicians of plotted values, quantitative analysis of changes in mean PEF values or within-day variability at and away from work, or computer-generated discriminant analysis (OASYS-2 freely available from www.occupationalasthma.com).[56] Visual analysis by experts seems to be the most sensitive method for identifying a pattern consistent with OA, but this method shows only moderate between- and within-expert agreement.[16] Computer-based interpretation of PEF recordings is helpful in overcoming such expert disagreements. Another limitation is that acceptable peak flow series are obtained in at most two-thirds of the subjects.

A systematic review of published studies found that PEF monitoring interpreted using computer-based discriminant analysis has a moderate sensitivity (82% [95% CI, 76%-90%]) but a high specificity (88% [95% CI, 80%-95%]) as compared with SIC and seems therefore more reliable in confirming than excluding OA.[56] Overall, self-recordings of FEV_1 have not been more accurate than PEF recordings.[57,58]

Serial measurements of NSBH. Comparative measurements of NSBH at work and at the end of a period (optimally, at least 2 weeks) away from the work exposure have been proposed to explore work-related asthma.[4] Changes in NSBH are usually considered significant when the PC_{20} value increases or decreases beyond the normal between-day variability of the test (usually, >2- to 3-fold changes). Few studies have investigated changes in NSBH at and off work in comparison with the results of SICs (Table III).[52-54] They reported highly variable rates of sensitivity (43%-62%) and specificity (52%-83%). Combining serial measurements of NSBH at and away from work with PEF monitoring showed only a slight improvement in sensitivity (84%-92%) over PEF recordings alone (81%-86%), with a decrease in specificity from 74%-89% to 61%-62%.[52,53]

TABLE V. Key messages for investigating subjects with possible OA

Procedure	Message
Ruling out OA	
Single assessment of NSBH	The absence of NSBH in subjects who have been recently exposed to the suspected workplace makes the diagnosis of OA highly unlikely (NPV >95%).
Single assessment of airway inflammatory markers	A normal FENO level and/or sputum eosinophil count make the diagnosis of OA highly unlikely in subjects removed from exposure who fail to demonstrate NSBH.
Ruling in OA	
Immunologic tests	• HMW agents: High sIgE titers provide a high specificity and PPV (>95%) for some allergens (wheat, rye, latex).
	• Combining NSBH with a positive SPT or sIgE for HMW and LMW agents test result increases the specificity (~85%) and PPV and may be considered confirmatory for probable OA when SIC is not available.
Serial assessment of PEF	• Serial PEF recordings provide moderate sensitivity (82% [95% CI, 76%-90%]) but high specificity (88% [95% CI, 80%-95%]) as compared with SIC result and are more reliable in confirming probable OA than excluding OA.
Serial assessment of sputum eosinophils	• Combining an increase in sputum eosinophils ≥3% at work with serial PEF measurements enhances the specificity of PEF, whereas the sensitivity is not significantly modified.

Serial assessments of sputum eosinophils. There is little information on whether the noninvasive assessment of airway inflammation at and away from work is helpful in establishing or excluding OA as compared with the result of an SIC. An increase in sputum eosinophils at 6- to 24-hour postchallenge has been documented in a substantial proportion of subjects with OA who develop an asthmatic reaction during SIC,[10,59] but only 1 study has evaluated the changes in sputum cell counts at work and away from work as compared with SIC results[54] (Table III). Using increasing cutoff values (ie, >1%, >2%, and >6.4%) for changes in sputum eosinophil percentage at and off work, these authors reported decreasing sensitivities (65%, 52%, and 26%, respectively) and increasing specificities (76%, 80%, and 92%, respectively). The addition of work-related changes in sputum eosinophil counts at and off work to serial PEF measurements enhanced the specificity of PEF analysis by 27% when using a cutoff increase in eosinophils at work of more than 2%, whereas the sensitivity was not significantly modified (Table III).[54]

Data collected during SICs indicate that an increase in sputum eosinophil counts induced by exposure to the causal agent more accurately reflects a positive SIC than does an increase in NSBH (Table III).[55] Combining a 2-fold or greater increase in postchallenge NSBH level or an increase in sputum eosinophil count of more than 3% achieved a sensitivity of 84% and a specificity of 74% with an NPV of 91% for the diagnosis of OA. Although blood eosinophil counts correlate with sputum eosinophilia and are increasingly used as a surrogate marker of airway inflammation, the changes in blood eosinophils after challenge exposure to occupational agents were unable to differentiate subjects with positive and negative SICs.[55]

Serial assessments of FENO. Measurement of FENO levels as a surrogate marker of eosinophilic airway inflammation is an easier and less time-consuming technique than sputum analysis.[33] Changes in FENO levels induced by exposure to occupational agents have been almost exclusively investigated during SIC procedures. In subjects with OA, an increase in FENO level occurs later (24 hours vs 6 hours) than an increase in sputum eosinophils after challenge exposure to the causal agent.[60] A recent study found that a postchallenge increase in FENO level of 17.5 ppb or more had a high specificity (90%) but a low sensitivity (45%) in predicting a positive SIC result and was predominantly associated with asthmatic reactions induced by HMW agents.[11] The usefulness of serial measurements of FENO levels at and off work has not been prospectively investigated although case reports have documented a possible role.[61-63] A recent retrospective study suggests that serial FENO measurements for 2 weeks off and at work provide complementary information in the diagnosis in about one-fifth of cases with suspected OA, especially when SIC is negative or cannot be performed.[64]

Specific inhalation challenges. SICs involve exposing workers to the suspected occupational agent in the controlled setting of a laboratory.[59] It is difficult to determine the validity of an SIC because there is no generally accepted "criterion standard" procedure against which this test can be compared. Nevertheless, the systematic review conducted by the Agency for Healthcare Research and Quality came to the conclusion that "there are probably no better alternatives (to SIC) in OA diagnosis at this time," but SIC should be considered a "reference standard" rather than the "criterion standard."[28] Indeed, the overall sensitivity of serial PEFs of about 80% compared with SIC indicates that PEF recordings will miss the diagnosis of OA in approximately 20% of workers as compared with SIC; conversely, serial PEF recordings may show work-related changes in about 20% of patients while the SIC is negative. This may be related either to false-negative SIC results (eg, reduced bronchial reactivity to the causal agent after prolonged removal from exposure or a wrong test agent) or to false-positive PEF recordings due to work-related changes in PEF resulting from nonspecific exposures at work rather than from specific causal agents.

A task force of the European Respiratory Society has issued recommendations for improving the safety and accuracy of an SIC,[59,65] so that the main remaining barrier to its use is the lack of available facilities for performing safe and accurate tests.[66,67] There are very few data on the relative cost-effectiveness of various diagnostic procedures in OA. Kennedy et al[68] found that

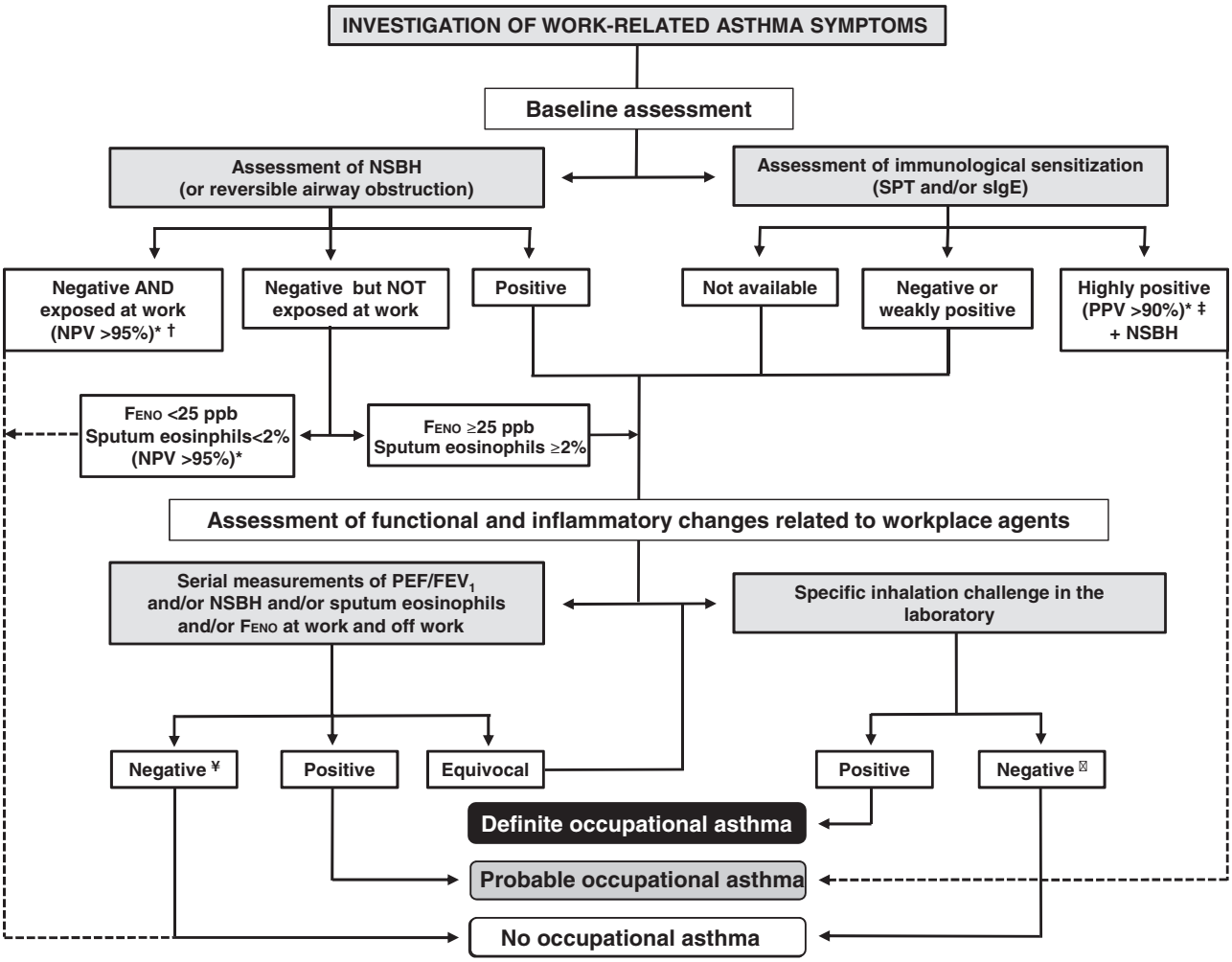

FIGURE 2. Proposed stepwise algorithm for diagnosing OA. *High NPV and PPV are applicable only to selected populations of subjects with a high pretest probability of OA (ie, tertiary centers). †Consider further investigation at the workplace if the clinical history is highly suggestive of OA because the absence of NSBH has been documented even after an asthmatic reaction induced by occupational agents.[29,30] ‡In subjects with NSBH when immunologic tests have been validated against SIC. Increasing the cutoff value for a positive sIgE test result of greater than or equal to 2.22 kU_A/L for wheat flour, greater than or equal to 9.64 kU_A/L for rye flour, and greater than or equal to 4.41 kU_A/L for latex provides a PPV for a positive SIC result higher than 95%. ¥Consider an SIC in the laboratory if the clinical history is highly suggestive of OA. #Consider a workplace inhalation challenge or serial PEF recording at work if the clinical history is highly suggestive of OA.

the SIC, used as the reference standard with an assumed 100% accuracy, was the most expensive technique, but correctly diagnosed 28% more patients with OA than the analysis of sputum cells collected at and off work, and 48% more patients than PEF monitoring. The indirect costs of an incorrect diagnosis of OA, resulting from unwarranted job changes and compensation, were not taken into account in this study but they are likely to outweigh the additional cost of SIC.

The European Respiratory Society Task Force[59] agreed that the broad categories of clinical indications for performing SIC with an occupational agent include (1) confirmation of the diagnosis of OA when other objective methods are not feasible, are less efficient, or have failed to provide definitive results and (2) identification of the cause of OA when other objective methods are not feasible, are less efficient, or have failed to provide definitive results. In addition, the SIC is an essential tool for the identification of new causal agents[7,69] and the characterization of underlying inflammatory mechanisms and phenotypic profiles, especially in OA induced by LMW agents such as multicomponent cleaning products and resins.[12,70,71]

Diagnostic algorithm. The selection of diagnostic tests to use in an individual patient depends on their employment status, the nature of the suspected workplace agent(s), available diagnostic facilities, and the purpose and potential consequences of the diagnostic evaluation. Key messages for diagnosing OA are presented in Table V, and an evidence-based stepwise approach for evaluating a subject with work-related asthma symptoms is proposed in Figure 2. The aim of such an approach is to restrict the use of expensive, time-consuming, or unavailable diagnostic

procedures to those subjects in whom the diagnosis of OA cannot be determined using other tests.

MANAGEMENT

The cornerstone of management is the control of further exposure to the inciting antigen.[4,16,18] Follow-up studies of subjects with OA indicate that persistent exposure to the causal agent is highly likely to result in the worsening of asthma and to show a faster rate of decline in FEV_1 and worsening of NSBH in comparison with those who avoid further exposure.[72-74] After complete avoidance of exposure to the causal agent, improvement in asthma symptoms and NSBH can continue for years after cessation of exposure, but the rate of improvement is steeper during the first 2.5 years.[75] However, complete avoidance of exposure, in the context of the published literature, reflects a change in occupation. Although the reported rates of full recovery after avoidance vary enormously, meta-analysis yield estimated rates of symptomatic recovery of 15% to 32% and persistence of NSBH of 67% to 73%.[74,76]

Several host- and exposure-related factors have been consistently found to influence the outcome of OA.[77] A higher level of airflow obstruction at the time of the diagnosis, a higher level of NSBH, a longer duration of symptomatic exposure, and an older age were associated with a worse outcome, emphasizing the importance of an early diagnosis of OA. In contrast, sex, atopy, and smoking status did not affect the outcome. The determinants of severe OA at the time of diagnosis have been investigated in a recent European multicenter cohort of subjects with OA.[78] This study identified potentially modifiable risk factors for severe OA (ie, persistently high level of exposure to the causal agent and duration of symptomatic exposure) that should be targeted to reduce the adverse impacts of the disease. Although follow-up studies suggested that subjects with OA due to HMW agents are more likely to have a worse outcome after complete avoidance of exposure to the causal agent,[76,77] the risk of severe OA at the time of diagnosis was not affected by the type of causal agent in this cohort. Nevertheless, subjects with OA due to LMW agents showed higher rates of severe exacerbations and a higher level of treatment compared with OA caused by HMW agents. The findings of this cohort study also highlighted host-related risk factors for severe OA (ie, a low level of education, a history of childhood asthma, and daily sputum production) that may help clinicians identify those subjects who have a higher risk of severe asthma. Interestingly, data collected in the subset of subjects who were already removed from exposure to the causal agent at the time of the diagnostic evaluation (median duration of removal, 7 months) showed a significant decrease in the prevalence of severe asthma from 18% to 11% and indicated that the persistence of severe asthma was then predominantly associated with individual sociodemographic and clinical factors (ie, daily sputum production, a low level of education, and obesity).

The health effects of exposure avoidance have to be set against the documented economic hardships of such decision, which frequently entail unemployment.[17,79] Reduction of exposure to the causal agent can be considered as an alternative with a lower socioeconomic impact than complete avoidance, but this approach seems to be less beneficial than complete cessation.[73,80] Some patients will prefer to remain in work, at least temporarily; this is easier for those in jobs with intermittent exposure (eg, to laboratory animals) rather than continuous exposure (eg, bakers). In these cases, they need to be advised about the risks they face, their exposures need to be minimized (using the hierarchical principles of exposure control), and they should be carefully monitored at regular intervals.

In all cases, symptoms of asthma should be managed using standard therapeutic approaches. There is limited evidence that the use of inhaled corticosteroids improves some aspects of recovery from OA after exposure avoidance.[74] There have been some reports of effective immunotherapy for a few agents causing OA, such as latex, flour, and laboratory animals.[81] A few reports suggested a beneficial effect of treatment with the monoclonal anti-IgE omalizumab on asthma control and exacerbations in patients who remained exposed to the causal agent,[82] although experience with "biological" asthma therapies is still very limited.

Worker's compensation schemes differ between jurisdictions.[83] Clinicians should be familiar with their local arrangements and advise their patients accordingly.

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