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DIAGNOSING OCCUPATIONAL ASTHMA

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Abbreviations

FeNO:	Exhaled nitric oxide
FEV ₁ :	Forced expiratory flow in one second
HMW:	High molecular weight
LMW:	Low molecular weight
NSBH:	Nonspecific bronchial hyperresponsiveness
NPV:	Negative predictive value
OA:	Occupational asthma
PEF:	Peak expiratory flow
PPV:	Positive predictive value
SIC:	Specific inhalation challenge
slgE:	Specific immunoglobulin E
SPT:	Skin prick test

Summary

Making an accurate diagnosis of occupational asthma (OA) is, generally, important. The condition has not only significant health consequences for affected workers, but also substantial socio-economic impacts for workers, their employers and wider society. Missing a diagnosis of OA may lead to continued exposure to a causative agent and progressive worsening of disease; conversely, diagnosing OA when it is not present may lead to inappropriate removal from exposure and unnecessary financial and social consequences. While the most accurate investigation is specific inhalation challenge in an experienced

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centre, this is a scarce resource and in many cases reliance is on other tests. This review provides a technical dossier of the diagnostic value of the available methods which include an appropriate clinical history, the use of specific immunology and measurement of inflammatory markers, and various methods of relating functional changes in airway calibre to periods at work. It is recommended that these approaches are used iteratively and in judicious combination, in cognisance of the individual patient's circumstances and requirements. Based on available evidence, a working diagnostic algorithm is proposed that can be adapted to the suspected agent, purpose of diagnosis, and available resources. For better or worse, many of the techniques – and their interpretation – are available only in specialised centres and where there is room for doubt, referral to such a centre is probably wise. Accordingly, the implementation or development of such specialised centres with appropriate equipment and expertise should greatly improve the diagnostic evaluation of work-related asthma.

Introduction

The workplace environment can lead to the development of different phenotypes of work-related asthma (1-3). It is now generally acknowledged that the term 'work-related asthma' encompasses both asthma caused by work (i.e. occupational asthma) and pre-existing or coincident asthma exacerbated by non-specific stimuli at work, the latter condition commonly referred to as 'work-exacerbated asthma' (WEA) (4). Occupational asthma (OA) may result either from immunologically-mediated sensitization to a specific substance at work (i.e. 'immunologic' OA or 'sensitizer-induced' OA) — hereafter simply referred to as OA — or from exposure(s) to high concentrations of irritant compounds (i.e., 'irritant-induced asthma'), best typified by the 'reactive airways dysfunction syndrome' (5).

The agents causing allergic OA include high-molecular-weight (HMW) (glyco)-proteins from vegetable and animal origin as well as low-molecular-weight (LMW) chemicals (6). HMW proteins and a few LMW compounds (i.e. platinum salts, reactive dyes, acid anhydrides, and some wood dusts such as obeche wood) appear to act through a type I, IgE-associated hypersensitivity mechanism (7), while for most LMW agents (e.g. isocyanates, persulphate salts, aldehydes, other wood dusts), the immunologic mechanism has not yet been fully characterized.

OA most often remains a diagnostic challenge for the clinician since there is no simple test that would allow for diagnosing the condition with a sufficiently high level of confidence. Instead, the diagnostic process has most often been to combine different procedures in a iterative process (1-3). Previous evidence-based guidelines (2, 3), consensus-based statements (1, 8), and review articles (9-11) have issued recommendations for the evaluation of work-related asthma, although consensus-based statements (1, 8) and review articles (9-11) failed to provide quantitative evidence supporting iterative testing schemes or combinations of diagnostic tests in order to guide a stepwise diagnostic approach. In addition, these documents recommended immunological testing to document IgE sensitization to occupational agents, but failed to incorporate the results of these tests in the diagnostic decision process.

The aim of this document was to critically analyze and summarize the available information on the validity and practical feasibility of diagnostic procedures in order to provide pragmatic guidance to clinicians who are faced with the management of work-related asthma symptoms. The final objective was to issue a simple working diagnostic algorithm (Figure 1) that can be adapted to the suspected agent, purpose of diagnosis, and available resources.

Why should occupational asthma be accurately diagnosed?

Complete avoidance of exposure to the causal agent is the recommended (1-3) and most effective (12-14) treatment option for OA. However, there is consistent evidence that OA is associated with prolonged unemployment and reduced income, particularly in subjects who completely avoid exposure to the offending agent (13, 15, 16). Therefore, 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 socio-economic impacts for workers, employers and the larger society. 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.

The possibility of OA should be thoroughly assessed, all the more so as work-related asthma symptoms are a frequent occurrence (~20%) among adult with asthma (17), although 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 (18, 19). In addition, a substantial proportion of subjects evaluated for work-related asthma-like symptoms fail to demonstrate any functional evidence of asthma (20).

Current issues in diagnosing OA

Available data worldwide indicate that work-related asthma remains largely unrecognized and inappropriately investigated. The diagnosis of OA is usually made 2 to 4 years after the onset of symptoms (21-24). Patients may not be aware of the work-relatedness of their symptoms or they may be reluctant to seek medical advice because of concerns about professional and financial consequences (21, 23, 25-27). However, recent surveys also identified a number of failures in both general and specialized medical practices. Health-care

practitioners do not systematically enquire about the temporal work-relatedness of asthma symptom and fail to identify potentially relevant occupational exposures (26, 28, 29). Primary care physicians delay referring patients with work-related symptoms to occupational or respiratory specialists for further assessment (22). Furthermore, secondary care chest physicians fail to perform objective diagnostic procedures to investigate the possible work-relatedness of asthma (22, 30).

Diagnostic procedures

Various tests are used in an effort to make a valid diagnosis of OA; they include the clinical history, assessment of nonspecific bronchial hyperresponsiveness (NSBH), immunological testing, and documentation of functional and inflammatory changes related to workplace exposure, specific inhalation challenge (SIC) with the suspected occupational agent(s) in the laboratory, and workplace inhalation challenge. The advantages and limitations of these tests are summarized in Table 1, while the available information on their validity is discussed below and detailed in Tables 2-6.

As is discussed later, the most accurate diagnosis of OA is made through SIC conducted in an experienced centre. Where SIC is not available or is considered not to be indicated, various other tests are used, generally in combination, to reach a sufficiently sound diagnosis. The certainty required may vary between patients with different circumstances; for example, it may be less important to reach a certain diagnosis in a patient who has already left the job in question and has no intention of seeking similar work in the future. Decisions about the necessary strength of a diagnosis should be discussed with the patient and may, of course, be coloured by issues around compensation which are likely to vary between different jurisdictions.

In most cases the assessments of test validity have been made, retrospectively, in populations of patients attending centres with a special interest in work-related asthma; in populations such as these the prevalence – and prior probability – of OA is high and the estimated predictive values of the various diagnostic tests may be lower in less selected patients such as those seen in primary or general secondary care. In addition, the sensitivity and specificity of diagnostic tests may be affected by the prevalence of OA in the studied populations (31, 32).

Clinical and occupational history

A typical history of OA includes the appearance or worsening of asthma symptoms at work and their disappearance or improvement away from work. However, this pattern is frequently obscured by the occurrence of late asthmatic reactions occurring after a work shift and asthma symptoms triggered by non-specific stimuli outside the workplace. In addition, when affected workers continue to be exposed to the sensitizing agent, remission of symptoms in the evenings or during weekends tends to disappear, and longer periods off work are necessary for symptom improvement.

The most relevant items that should be addressed when taking the clinical history include: occupation (description of tasks and processes and identification, through familiarity, expert advice or examination of Material Safety Data Sheets, of direct and indirect exposures to potential workplace asthmagens (6) (http://occupationalasthma.com/occupational_asthma_causative_agents.aspx, last accessed September 29, 2016 and www.eaaci.org/images/files/Pdf_MsWord/2010/occupational_allergens, last accessed September 29, 2016) respiratory symptoms (nature, latency period, temporal relationship with work exposure, especially during the early period after symptom onset); and associated work-related disorders (rhinitis/conjunctivitis; urticaria, contact dermatitis). Of note, asthma symptoms are commonly accompanied and often preceded by

work-related rhinitis and conjunctivitis symptoms, especially when HMW agents are involved (33, 34).

Available data clearly indicate that the clinical history has a high sensitivity but a low specificity for diagnosing OA (Table 2) (18, 19, 35, 36). In a large cohort of patients evaluated for possible OA in tertiary centers, wheezing at work and work-related nasal and ocular itching were associated with the highest specificity for OA (Table 2) (19). Establishing a diagnosis of OA therefore requires further objective documentation of the causal relationship between asthma and the suspected work environment.

Assessment of nonspecific bronchial hyperresponsiveness

It has generally been recommended that the first diagnostic step should be to confirm the presence of asthma through the demonstration of reversible airflow obstruction or increased NSBH to methacholine or histamine in subjects without airflow limitation (1, 11). However, the presence of NSBH has a low specificity (48-64%) and accordingly a low positive predictive value (PPV) for diagnosing OA (55-62% among workers evaluated for possible OA in tertiary centres) (Table 3) (37-39). On the other hand, the presence of NSBH showed reasonable sensitivity (84%) and NPV (75%) in predicting the outcome of a SIC (Table 3). Therefore, it has been assumed that the absence of NSBH *“has a fairly high negative predictive value (NPV) for current symptomatic asthma, and generally can be used to rule out active disease”* (1). However, a number of studies have shown that NSBH may improve rapidly and even return to normal, sometimes within a few days, after cessation of exposure to the offending agent (40-43) and may recur on re-exposure (44, 45). A recently published retrospective study of a large cohort of subjects investigated for OA through a SIC found that being still at work at the time of SIC and treatment with inhaled corticosteroid were the most significant predictors for the presence of increased NSBH among subjects with a positive SIC (odds ratio of 2.7 [95% CI, 1.2-5.9] and 6.2 [95%CI, 2.7-14.4], respectively) (39). This

study further demonstrated the importance of measuring NSBH when the subject is still exposed at work since the sensitivity of the test increased from 67% when the subjects were off work at the time of assessment to 98% when NSBH had been assessed at least once when they were still at work (Table 3). In this cohort of subjects investigated in a tertiary centre, the NPV increased from 82% off work to 98% when NSBH was measured while exposed at work.

These data indicate that the presence of NSBH is insufficient to establish a diagnosis of OA, while its absence when the subject has been recently exposed (i.e. within 24 hours) to the suspected workplace makes the diagnosis of OA highly unlikely. Nevertheless, there have been reports of normal NSBH both before and after a positive SIC (46). In the above-quoted study, Pralong et al. further characterized 23 out of 278 subjects with a positive SIC who failed to demonstrate NSBH both before and after the SIC (39). Eleven of these 23 subjects had an increased NSBH on at least one occasion when they had been evaluated while exposed at work.

Immunological testing

Skin prick tests (SPT) and assessment of serum specific IgE (sIgE) antibodies are useful to demonstrate IgE-mediated sensitization to most HMW and some LMW occupational agents (anhydride acids, platinum salts, reactive dyes, obeche wood), although a positive test does not necessarily imply that the subject has OA. Unfortunately, there is a lack of standardization and validation for most available extracts of occupational agents and the allergenic potency of SPT extracts may vary significantly among manufacturers (47-49). Available information on the sensitivity and specificity of immunological tests for occupational agents is summarized in Table 4 (36, 37, 50-52). Recent studies showed that increasing the cut-off value for a positive sIgE test (i.e. ≥ 2.22 kU_A/l for wheat flour, ≥ 9.64 kU_A/l for rye flour, and ≥ 5.41 kU_A/l for latex) increased the specificities and PPVs above 95% (50, 51). Hannu

et al. reported that a SPT response to obeche wood dust ≥ 3.5 mm yielded a specificity and PPV of 100% with a sensitivity of 67% as compared to SIC (52).

More recently, the usefulness of measuring sIgE antibodies against the recombinant allergen components of flour and latex has been investigated (51, 53). Combining the presence of sIgE against some recombinant allergens of *Triticum aestivum* (Tri a) 27, 28, 29.02, 32 and 39 provided a high specificity (97%) with a sensitivity of 70% for wheat flour allergy among bakers (53). In addition, Bittner et al. (54) reported that 21 (49%) of 43 subjects with baker's asthma who showed a negative sIgE result to a commercial wheat flour extract demonstrated sIgE reactivity against at least one of six newly identified wheat recombinant proteins. Vandenplas et al. (51) found that the sum of sIgE concentrations against the recombinant allergens of *Hevea Brasiliensis* (rHev b) 5 and rHev b 60.1 or 6.02 yielded a high predictive value ($>95\%$) for a positive SIC similar to that provided by the level of sIgE against the whole latex extract, but with a higher sensitivity (79%) and diagnostic efficiency (0.67) as compared with latex-sIgE (49% and 0.41, respectively). Interestingly, high levels of sIgE antibodies against NRL or rHev b 5 plus rHev b 60.1/6.02 showed a high PPV for a positive SIC with latex independently from the presence of NSBH at baseline. Among positive SICs, NSBH was absent at baseline assessment in 4 of 40 subjects with sIgE against NRL ≥ 5.41 kU_A/l and in 6 of 65 subjects with a sIgE titer against rHev b 5 plus rHev b 60.1/6.02 ≥ 1.46 kU_A/l. All these subjects showed a level of NSBH in the asthmatic range after the positive SIC. Such information on NSBH was not available in the studies on bakers' asthma (50). Nevertheless, measurement of sIgE antibodies against the tested panel of recombinant latex allergen components did not improve the NPV of immunological testing since none of the subjects with a positive SIC and a negative sIgE against the whole latex extract showed IgE reactivity to allergen components.

In subjects exposed to LMW agents, the sensitivity of sIgE determination is usually low (31% [95% CI, 23-41%]) while the specificity is high (89% [95% CI, 85-92%]) (37) (Table 4). SPT with LMW agents should be performed with caution since allergenic extracts are not

standardized and most of these agents are potentially irritant to the skin and may produce false-positive results (55).

Combining the presence of NSBH with a positive SPT or sIgE test increased markedly the specificity of NSBH assessment alone, while sensitivity was inconsistently modified (36, 37) (Table 6).

Serial measurements of peak expiratory flow/FEV₁

The few available data indicate that comparison of before and after shift measurements in FEV₁ (56) or peak expiratory flow (PEF) (57) is an unreliable procedure for identifying OA. Cross-shift changes in FEV₁ and PEF can show a high specificity (91%) (57), but have a low sensitivity (50-60%) (56, 57).

More intensive serial PEF recording during periods at and off work is helpful to investigate objectively the relationship between workplace exposure and changes in airway caliber, as illustrated in Figure 2 (2). The work-relatedness of PEF values can be evaluated through visual inspection of plotted values by “experts”, quantitative analysis of changes in mean PEF values or within-day variability at work and away from work, or computer-generated discriminant analysis (OASYS-2; OASYS Research Group, Midland Thoracic Society, Birmingham, UK) (58, 59). Visual analysis by experts seems to be the most sensitive method for identifying whether a PEF record shows a pattern consistent with OA, but it has been found to show only moderate between- and within- expert agreement (2). Computer-based interpretation of PEF records is helpful in overcoming such expert disagreements. Self-recordings of FEV₁ have not been more accurate than the PEF recordings (60, 61).

A systematic review published in 2010 found a pooled sensitivity from all studies of 75% and a pooled specificity of 79% (Table 5) (58). When the analysis was restricted to PEF records fulfilling the minimum data quantity, the sensitivity was slightly increased at 82% and the

specificity at 88%. Visual analysis yielded a sensitivity (78%) equivalent to computer-based analysis (71%), but with a lower specificity (69%) compared to computer-based analysis (91%). Overall, PEF monitoring interpreted using computer-based discriminant analysis has a moderate sensitivity but a high specificity as compared to SIC and seems therefore more reliable in confirming than excluding OA.

Serial measurements of nonspecific bronchial responsiveness

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 recommended to explore work-related asthma (1-3). Changes in NSBH are usually considered significant when the provocative concentration/dose of methacholine or histamine causing a 15 or 20% fall in FEV₁ (PC/PD_{15/20}) increases or decreases beyond the normal between-day variability of the test (usually, >2- to 3-fold changes) from one assessment to the next.

Four studies, all from Canadian centres, investigated changes in NSBH at and off work with comparison to the results of SICs (Table 5) (62-65). Three of these studies were prospective (63-65), but one failed to provide the information on work-related changes in NSBH alone (65). One study had a retrospective design where serial assessments of NSBH were not systematically completed (62). Using different threshold changes in PC₂₀ values, these studies reported highly variable sensitivity (43% to 62%) and specificity (52% to 83%) rates. Based on these data, it has been concluded that “*changes in NSBH at and away from work alone have only moderate sensitivity and specificity for the diagnosis of OA*” (2, 3). Combining serial measurements of NSBH at work and away from work with PEF monitoring showed only a slight improvement in sensitivity over PEF recordings alone, with a decrease in specificity (Table 6) (63, 64).

Serial assessments of airway inflammation

Non-invasive methods for the evaluation of airway inflammation, including sputum eosinophil count and measurement of exhaled nitric oxide (FeNO), have been proposed for the investigation of work-related asthma (66).

Sputum eosinophils

Only one study provided information on the usefulness of a single assessment of sputum eosinophils in predicting the outcome of SIC (38). A baseline eosinophil count $\geq 3\%$ yielded a sensitivity of 29% and a specificity of 86%. In this selected population, the PPV was low (41%) while the NPV was high (82%), figures that were similar to those provided by a baseline assessment of NSBH. Sputum eosinophil count is however useful for identifying non-asthmatic eosinophilic bronchitis caused by workplace agents (67, 68).

Although an increase in sputum eosinophils at 6-24 hour post-challenge has been documented in a substantial proportion of subjects with OA who develop an asthmatic reaction during SIC with the causal agent (69-71), only one study has evaluated the changes in sputum cell counts at work and away from work as compared to SIC results (65). Using increasing cut-off values (i.e. $>1\%$ point, $>2\%$ and $>6.4\%$) for changes in sputum eosinophil percentage at work and off work, these authors found decreasing sensitivity rates (65%, 52% and 26%, respectively) and increasing specificities (76%, 80% and 92%, respectively) (Table 5). The addition of changes in sputum eosinophil counts at work and off work to serial PEF measurements enhanced the specificity of PEF analysis by 27% when using a cut-off increase in eosinophils at work of more than 2%, while the sensitivity was not significantly modified (Table 6) (65). Notably, this study reported unusually low values of sensitivity (35%) and specificity (65%) of PEF records analyzed using OASYS 2 in comparison to SIC (65).

Exhaled nitric oxide

Measurements of the fractional exhaled nitric oxide (FeNO) concentration as a surrogate marker of eosinophilic airway inflammation is an easier and less time-consuming technique than sputum analysis, but available studies have provided inconsistent results in the investigation of OA (66). In subjects with OA, an increase in FeNO occurs later (24 h vs. 6 h) than an increase in sputum eosinophils after challenge exposure to the causal agent (69, 72). A recent study found that a post-challenge increase in FeNO levels ≥ 17.5 ppb was associated with a positive SIC with a high specificity of 90% but a low sensitivity of 45% (73). Although assessment of FeNO may aid in the interpretation of SIC (74), the usefulness of serial measurements of FeNO at work and off work has not been prospectively investigated; only a few case reports have documented a possible role for this procedure (75-77).

Specific inhalation challenge

SICs involve exposing workers to the suspected occupational agent in the controlled setting of a laboratory in order to investigate empirically the specific reactivity of the airways to occupational agents (71). It is, however, difficult to determine the validity of SIC because there is no generally accepted “gold standard” procedure against which these test can be compared. Nevertheless, the systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) came to the conclusion that *“In isolation, none of the other diagnostic tests yielded a sufficiently high combination of sensitivity and specificity that they could replace SIC”*, while stepwise combinations of these diagnostic tests have not been evaluated in sufficient detail to provide evidence-based recommendations (12, 37).

The AHRQ review concluded 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 “gold standard”, while the British Occupational Health Research Foundation acknowledged that: *“A carefully controlled SIC comes closest to a gold standard test for some agents*

causing OA" (2). Discordant results between PEF recordings and SIC warrant further investigation. Indeed, the overall sensitivity of serial PEFs of about 80% compared to SIC (12, 37, 58) means that PEF recordings will miss the diagnosis of OA in ~20% of workers as compared to SIC. Conversely, serial PEF records may show work-related changes while the SIC is negative in about 20% of patients. This may be related either to false-negative SIC result (e.g. reduced bronchial reactivity to the causal agent after prolonged removal from exposure or a wrong test agent) or to false-positive PEF records due to work-related changes in PEF resulting from non-specific exposures at work rather than specific causal agents.

A Task Force of the European Respiratory Society has recently issued recommendations for improving the safety and accuracy of SIC (71), so that the main remaining barrier to its use is the lack of available facilities for performing safe and accurate tests (78) and the cost of the procedure. There are very few data on the relative cost-effectiveness of various diagnostic procedures in OA. Kennedy and co-workers (79) found that the SIC, used as the reference standard with an assumed 100% accuracy, was the most expensive technique, but correctly diagnosed 28% more OA patients than the analysis of sputum cells collected at work and off work, and 48% more patients than PEF monitoring. The costs resulting from an incorrect diagnosis of OA, leading to unwarranted job changes and compensation, were not taken into account but are likely to outweigh the additional cost of SIC.

The European Respiratory Society Task Force (71) agreed that the broad categories of indications for performing SIC with an occupational agent include: *1) confirmation of the diagnosis of occupational asthma when other objective methods are not feasible, are less efficient or have failed to provide definitive results; 2) identification of the cause of occupational asthma when other objective methods are not feasible, are less efficient or have failed to provide definitive results; 3) the identification of a new (not formerly described) specific cause of occupational asthma; and 4) research into the mechanisms of work-related asthma.*

Workplace challenges

Workplace challenge involves serial FEV₁ measurements that are supervised by a technician before and throughout a work shift. This test should also include a control day without occupational exposure in order to evaluate spontaneous variations in FEV₁. There are very few data on the validity of these tests as compared to SIC in the laboratory. In one retrospective series, workplace challenge was positive in 22% of workers with a negative SIC but a clinical history highly suggestive for OA and complex workplace exposures (i.e. more than one potential sensitising agent at work) (80). Currently, inhalation challenges at the workplace should be considered mainly when both PEF records and SIC are inconclusive.

Proposed 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. Accordingly, an evidence-based, practical approach for evaluating a subject with work-related asthma symptoms is summarized in Figure 1.

The main issue in clinical practice is to differentiate OA from WEA. According to an American Thoracic Society Statement (4), the diagnosis of WEA relies on the demonstration of a relationship between occupational exposures and the occurrence of asthma exacerbations or poor asthma control during periods at work combined with the ascertainment that OA is unlikely. Serial PEF monitoring can show increased variability during periods at work compared to periods away from work in subjects with OA compared with WEA, although this procedure failed to reliably differentiate these two conditions using the visual interpretation or the computerized analysis of PEF graphs (81). Based on sputum

analysis, a non-eosinophilic phenotype has been more often documented in subjects with WEA compared to those diagnosed as OA according to the results of SIC (82). SIC in the laboratory or at the workplace associated with the measurement of inflammatory markers may be used as an attempt to distinguish sensitizer-induced OA from WEA, although challenge tests with irritant substances are still poorly standardized (71). In the differential diagnosis, other conditions, such as vocal cord dysfunction, hyperventilation syndrome, and multiple chemical sensitivity syndrome, should be carefully considered, especially since these “asthma-mimics” may also result from exposure to irritants in the workplace (1).

Unmet needs and future requirements

Since a late diagnosis of OA is associated with a poor outcome, efforts should be made to increase the awareness of OA in primary care practice. A crucial step for enhancing the diagnosis of OA is to promote the prompt referral of workers suspected of having OA to specialists who have the expertise and facilities for performing appropriate investigations.

The development of specialized centres with appropriate equipment, expertise, and financial resources to complete thorough diagnostic assessment of work-related asthma should become a priority.

The diagnosis of OA would greatly benefit from the implementation of international multicentre studies aimed at evaluating the validity and cost-effectiveness of different diagnostic approaches for assisting physicians and policy makers in elaborating rationale strategies.

Legend to Figures

Figure 1

Proposed stepwise diagnostic algorithm for occupational asthma. FEV₁: forced expiratory flow in one second; NSBH: nonspecific bronchial hyperresponsiveness; NPV: negative predictive value; OA: occupational asthma; PEF: peak expiratory flow; PPV: positive predictive value; sIgE: specific immunoglobulin E; SPT: skin-prick test.

* High NPV and PPV are applicable only to selected populations of subjects with a high pre-test probability of OA (i.e. tertiary centres).

† Consider assessment of sputum eosinophils to identify occupational non-asthmatic eosinophilic bronchitis or further investigation if the clinical history is highly suggestive of OA.

‡ In subjects referred for possible occupational asthma when immunological tests have been validated against specific inhalation challenge (i.e. flour, latex, and obeche wood). In subjects with highly positive immunological testing for these agents but a negative NSBH test, the second-step investigations should still be performed.

¥ Consider specific inhalation challenge in the laboratory if the clinical history is highly suggestive of occupational asthma.

Consider workplace inhalation challenge or serial PEF recording if the clinical history is highly suggestive of occupational asthma.

Figure 2

A four-week series of peak flow measurements completed by a baker with occupational asthma attributed to wheat flour. Each column represents a day, those that are shaded are days at work. On each day the maximum, mean and minimum values of peak flow are plotted; the figures in the boxes at the head of each column are for diurnal variability. The

horizontal line is the 'predicted' peak flow based on his age and height. There is clear pattern of work-related asthma with recovery on days away from work.

Table 1. Advantages and limitations of diagnostic tests used in the investigation of occupational asthma

Diagnostic test	Advantages	Limitations
Assessment of NSBH	• Low cost. • Confirms the diagnosis of asthma. • A negative test in recently exposed subjects makes the diagnosis very unlikely (39).	• May not be widely available in some countries. • Low specificity for diagnosing OA (39).
Immunological tests	• Low cost. • Demonstrate IgE sensitization but not OA. • High levels of sIgE have a documented high positive predictive value for OA due to flour and latex (50, 51).	• Commercial extracts for sIgE lacking for most LMW agents • Extracts for SPT and sIgE not standardized for most HMW agents, except for latex (49)
Serial assessments of work-related changes in PEF	• Low cost. • Does not require specific equipment and can be used in any healthcare setting. • Assessment during usual work exposure. • Possible fabrication of results can be prevented by data-logging instruments. • Computer-based analysis tool available for plotting and interpretation (www.occupationalasthma.com). • Computer-based analysis overcomes within- and between-observer variability.	• Impossible to perform when the worker has already been definitively removed from exposure. • Not suitable in subjects with a history of severe work-related reactions. • Measurements are effort-dependent. • Requires careful instruction and training of subjects. • Requires subjects' collaboration for measurements during prolonged periods. • Sensitivity and specificity affected by the method used to interpret the records and asthma medication (58). • Minimum criteria for optimal validity of computer-based analysis: ≥ 4 readings a day with ≥ 3 consecutive workdays in any work period and ≥ 3 complexes (about three weeks) (83). • Minimum criteria for optimal validity of visual analysis: ≥ 4 readings a day for at least 2 weeks at work and 2 weeks away from work (84). • Recording at and away from work may be difficult to arrange and may imply indirect costs. • Acceptable and interpret table recordings obtained in ~60% of subjects % (24, 58). • Visual interpretation of the results requires expertise.

		No precise identification of the causal agent.
Serial assessments of work-related changes in sputum eosinophils	- Impossible to falsify. - Bring additional evidence to the diagnosis of OA.	- Expensive and time-consuming. - Requires standardized methodology and qualified technologist. - Not widely available - Substantial (~25%) proportion of subjects fail to produce suitable sputum samples. - Does not itself allow for confirmation or exclusion of the diagnosis of OA.
Serial assessments of work-related changes in exhaled NO	- Noninvasive - Easy to perform, rapid	- Inconsistent results. - Difficult to interpret. - Affected by many different factors (e.g., smoking, inhaled corticosteroids).
Specific-inhalation challenge in the laboratory	Still considered the “reference” method for the diagnosis of OA and the identification of causal agent.	- Expensive. - Time-consuming. - Available in a limited number of centers (78). - May induce severe asthmatic reactions (85, 86) - False negative tests are possible and require stringent methodology and use of sensitive indices of airway response (71) - Complex work exposures may not be reproduced in the laboratory.
Workplace inhalation challenge	- Excludes OA if negative when performed in the usual work conditions. - May help to confirm OA when SIC are not feasible due to complex workplace exposures or absence of identified sensitizer at work.	- Much more expensive than SIC. - No precise identification of the causal agent. - Requires authorization from the employer for performing the measurements at work. - Concomitant exposure to irritants at the workplace cannot be controlled.

Table 2. Validity of the clinical history

Causal agent	Prevalence of OA*	Outcome	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Reference
Various	75/162 (46%)	Global clinical history :	87	22	63	83	<i>Malo, 1991 (18)</i>
Latex	31/45 (69%)		87	14	75	50	<i>Vandenplas, 2001 (35)</i>
Latex	19/30 (63%)		89	50	77	71	<i>Quirce, 2003 (36)</i>
Various	72/212 (34%)	Sx worse at work	90	8	37	63	<i>Vandenplas, 2005 (19)</i>
		Sx worse on specific exposure	75	21	33	62	
		Sx improvement during vacations	74	57	57	74	
		Wheezing at work	40	85	89	32	
		Nasal itching at work	48	74	53	70	
		Ocular itching at work	41	72	58	56	

Legend: Sx: symptoms.

* OA defined by a positive specific inhalation challenge

Table 3. Validity of nonspecific bronchial hyperresponsiveness assessment

Single assessment of NSBH	Prevalence of OA*	Sensitivity (%) [†]	Specificity (%) [†]	Positive Predictive Value (%)	Negative Predictive Value (%)	Reference
Various agents [‡]	202/428 (47%)	84 (67-93%)	48 (26-72%)	55	75	<i>Beach, 2007 (37)</i>
HMW agents [‡]	126/252 (50%)	79 (68-88)	51 (35-67)	62	73	
LMW agents [‡]	424/1071 (40%)	67 (58-74)	64 (56-71)	56	75	
At baseline of SIC (various agents)	129/519 (25%)	73	51	33	85	<i>Malo, CEA 2011 (38)</i>
At baseline of SIC (various agents)	278/1012 (28%)	80	47	36	86	<i>Lemière, 2016 (39)</i>
At baseline while still exposed at work (various agents)	131/430 (30%)	95	40	41	95	
At baseline while off work (various agents)	147/582 (25%)	67	52	32	82	
At least one assessment during work exposure (various agents)	157/479 (33%)	98	39	44	98	

Legend: HMW: high molecular weight; LMW: low molecular weight; NSBH: nonspecific bronchial hyperresponsiveness; SIC: specific inhalation challenge.

* OA defined by a positive specific inhalation challenge;

[†] 95% confidence interval within parentheses when available;

[‡] In the meta-analysis by Beach and coworkers, the time elapsed between the last work exposure and NSBH assessment was not available; the prevalence of OA and the predictive values of a single NSBH assessment were derived from the figures provided in reference (12).

Table 4. Validity of immunological tests

Agent	Test	Prevalence of OA*	Sensitivity (%) [†]	Specificity (%) [†]	Positive Predictive Value (%) [†]	Negative Predictive Value (%) [†]	Reference
HMW agents:							
Various	SPT [‡]	175/434 (40%)	81 (70-88)	60 (42-75)	73	81	<i>Beach, 2007 (37)</i>
	slgE [‡]	113/246 (46%)	73 (64-81)	79 (50-93)	86	82	
Flour, wheat	SPT	37/71 (52%)	68	74	74	68	<i>Van Kampen, 2008 (50)</i>
	slgE [£] ≥0.35 kU _A /l	37/71 (52%)	87	68	74	82	
	slgE [£] ≥2.22 kU _A /l	37/71 (52%)	51	100	100	65	
Flour, rye	SPT	63/95 (66%)	78	84	91	66	
	slgE [£] ≥0.35 kU _A /l	63/95 (66%)	87	62	82	71	
	slgE [£] ≥9.64 kU _A /l	63/95 (66%)	30	100	100	42	
Latex	SPT	19/30 (63%)	100	20	70	100	<i>Quirce, 2003 (36)</i>
	slgE [£]	19/30 (63%)	95	40	75	80	
	slgE [£] ≥0.35 kU _A /l	85/107 (79%)	94 (86-98)	48 (28-72)	86 (77-92)	71 (44-90)	<i>Vandenplas, 2016 (51)</i>

	slgE [£] ≥4.41 kU _A /l	85/107 (79%)	49 (38–60)	92 (74–99)	95 (84–99)	35 (24–48)	
<i>LMW agents :</i>							
Various	slgE	NA	31 (23-41)	89 (85-92)	NA	NA	<i>Beach, 2007 (37)</i>
	SPT [†] §	69/215 (32%)	73 (60-83)	86 (77-92)	75	89	
Obeche wood	SPT ≥3 mm	27/34 (79%)	74 (59-89)	86 (74-98)	95 (88-102)	54 (37-71)	<i>Hannu, 2013 (52)</i>
	SPT ≥3.5 mm		67 (51-83)	100 (100-100)	100 (100-100)	56 (39–73)	

Legend: HMW: high molecular weight; LMW: low molecular weight; NA: not available; SIC: specific inhalation challenge; slgE: specific IgE antibodies; SPT: skin-prick test.

* OA defined by a positive specific inhalation challenge;

† 95% confidence interval is given within parentheses when available;

‡ In the meta-analysis by Beach and coworkers, the prevalence of OA and the predictive values of immunological tests were derived from the figures provided in reference (12)..

§ SPT with low molecular weight agents included reactive dyes, green tea, bleaching powder, and exotic wood dusts.

£ Commercial assay (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden)

Table 5. Validity of serial measurements of lung function tests and airway inflammation

Serial testing at work and off work	Prevalence of OA	Sensitivity (%) [*]	Specificity (%) [*]	Reference
PEF (various agents) [*]	5 ^{†‡}	64 (43-80)	77 (66-85)	<i>Beach, 2007 (37)</i>
PEF (various agents; all records)	16-14 [‡]	75 (69-81)	79 (73-87)	<i>Moore, 2010 (58)</i>
PEF (records with minimum data quantity)	8 [‡]	82 (76-90)	88 (80-95)	
PEF (computer-based analysis)	6 [‡]	71 (54-85)	91 (78-99)	
PEF (visual analysis)	9 [‡]	78 (72-85)	69 (64-86)	
NSBH (various agents, >4-fold change in PC ₂₀)	9/15 (60%) [†]	56	83	<i>Tarlo, 1990 (62)</i>
NSBH (red cedar, >2-fold change in PC ₂₀)	14/23 (61%) [†]	62	78	<i>Côté, 1990 (63)</i>
NSBH (various agents, >2-fold change in PC ₂₀)	25/61 (41%) [†]	61	52	<i>Perrin, 1992 (64)</i>
NSBH (various agents, >3.2-fold change in PC ₂₀)		43	65	
Sputum eosinophils, increase at work >1%	23/45 (51%) [†]	65 (45-81)	76 (57-88)	<i>Girard, 2004 (65)</i>
Sputum eosinophils, increase at work >2%		52 (33-71)	80 (61-91)	
Sputum eosinophils, increase at work >6.4%		26 (13-46)	92 (75-98)	

Legend: PEF: peak expiratory flow rate; NSBH: non-specific bronchial hyperresponsiveness; PC₂₀: provocative concentration of methacholine/histamine inducing a 20% fall in FEV₁.

^{*} 95% confidence interval is given within parentheses when available

[†] SIC used as the confirmatory test for occupational asthma;

[‡] Number of studies included in the meta-analysis (number of subjects and prevalence of OA not available);

Table 6. Validity of combined diagnostic tests

Serial testing at work and off work	Prevalence of OA	Sensitivity (%) [*]	Specificity (%) [*]	Reference
NSBH alone (latex)	19/29 (66%) [†]	90	10	<i>Quirce, 2003 (36)</i>
NSBH + SPT(latex)		84	70	
NSBH + SPT (HMW agents)	NA [‡]	61 (21-90)	82 (54-95)	<i>Beach, 2007 (37)</i>
NSBH + sIgE (HMW agents)	NA [‡]	36 (1-96)	85 (48-97)	
PEF alone (red cedar)	14/23 (61%) [†]	86	89	<i>Côté, 1990 (63)</i>
PEF + NSBH		92	62	
PEF alone (various agents)	25/61 (41%) [†]	81	74	<i>Perrin, 1992 (64)</i>
PEF + NSBH (>2-fold change in PC ₂₀)		84	61	
PEF alone (computer-based analysis) (various agents)	23/45 (51%) [†]	35 (19-55)	65 (45-81).	<i>Girard, 2004 (65)</i>
PEF alone (visual analysis by 5 experts)		63-87	48-62	
NSBH alone (>2-fold change in PC ₂₀)		NA	NA	
PEF (visual analysis) + NSBH		60-88	37-62	
PEF + sputum eosinophils >1%		50 (24-76)	75 (51-90)	
PEF + sputum eosinophils >2%		36 (15-65)	80 (55-93)	

Legend: PEF: peak expiratory flow rate; NA: not available; NSBH: non-specific bronchial hyperresponsiveness; PC₂₀: provocative concentration of a pharmacologic agent inducing a 20% fall in FEV₁; SPT: skin-prick test.

^{*} 95% confidence interval is given within parentheses when available

[†] SIC used as confirmatory test for occupational asthma;

[‡] Number of subjects and prevalence of OA not available.

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