Evidence based guidelines for the prevention, identification, and management of occupational asthma


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Evidence based guidelines for the prevention, identification, and management of occupational asthma


Background: Occupational asthma is the most frequently reported work related respiratory disease in many countries. This work was commissioned by the British Occupational Health Research Foundation to assist the Health and Safety Executive in achieving its target of reducing the incidence of occupational asthma in Great Britain by 30% by 2010.

Aim: The guidelines aim to improve the prevention, identification, and management of occupational asthma by providing evidence based recommendations on which future practice can be based.

Methods: The literature was searched systematically using Medline and Embase for articles published in all languages up to the end of June 2004. Evidence based statements and recommendations were graded according to the Royal College of General Practitioner’s star system and the revised Scottish Intercollegiate Guidelines Network grading system.

Results: A total of 474 original studies were selected for appraisal from over 2500 abstracts. The systematic review produced 52 graded evidence statements and 22 recommendations based on 223 studies.

Discussion: Evidence based guidelines have become benchmarks for practice in healthcare and the process used to prepare them is well established. This evidence review and its recommendations focus on interventions and outcomes to provide a robust approach to the prevention, identification, and management of occupational asthma, based on and using the best available medical evidence. The most important action to prevent cases of occupational asthma is to reduce exposure at source. Thereafter surveillance should be performed for the early identification of symptoms, including occupational rhinitis, with additional functional and immunological tests where appropriate. Effective management of workers suspected to have occupational asthma involves the identification and investigation of symptoms suggestive of asthma immediately they occur. Those workers who are confirmed to have occupational asthma should be advised to avoid further exposure completely and early in the course of their disease to offer the best chance of recovery.

Work related asthma, where there is an association between symptoms and work, includes: work aggravated asthma (pre-existing or coincidental new onset asthma worsened by workplace exposure); and occupational asthma (OA; new onset asthma caused by workplace exposure). OA can be either: hypersensitivity induced OA characterised by latency between first exposure to a substance at work and the development of symptoms; or irritant induced OA that occurs shortly after a high exposure to an irritant gas, fume, or vapour at work. Almost 90% of cases of occupational asthma are of the hypersensitivity type and are the focus for this review.

This review was commissioned and funded by the British Occupational Health Research Foundation (BOHRF) to provide a robust approach to the prevention, identification, and management of OA, based on and using the best available medical evidence.

METHODS

We systematically searched Medline and Embase from 1966 and 1974 respectively to the end of June 2004. Pairs of working group members reviewed over 2500 abstracts independently to select 474 papers for further, independent critical review; single case studies and narrative reviews were excluded. Data from 223 papers were entered into evidence tables and contributed to the evidence statements.

Criteria for grading evidence and recommendations were developed primarily to guide inferences about treatment; questions about disease frequency, aetiology, diagnosis, and prognosis require other hierarchies. There are few meta-analyses and randomised controlled trials (RCTs) related to OA, and so little Scottish Intercollegiate Guidelines Network (SIGN) grading system level 1 evidence. Therefore we graded evidence statements (ES) and recommendations using both the revised SIGN grading system 2000 for levels of evidence (table 1) and recommendations (table 2), and the modified 1995 Royal College of General Practitioners (RCGP) three star system used in the BOHRF Occupational Health Guidelines for the Management of Low Back Pain at Work (table 3). In accordance with current opinion, recommendations appear in behaviourally specific terms.

RESULTS AND DISCUSSION

Background

OA is the most frequently reported occupational respiratory disorder in westernised industrialised populations. Where mining is common, for example, South Africa and the Czech Republic, OA is the second commonest occupational respiratory disorder after pneumoconiosis.

Abbreviations: BOHRF, British Occupational Health Research Foundation; ES, evidence statement; HMW, high molecular weight; LMW, low molecular weight; OA, occupational asthma; PEF, peak expiratory flow; RCT, randomised controlled trial; RCGP, Royal College of General Practitioners; RPE, respiratory protective equipment; SIGN, Scottish Intercollegiate Guidelines Network; SBPT, specific bronchial provocation testing.
There are no complete registries of OA so the true frequency of the disease is unknown. Published frequencies come from surveillance schemes, compensation registries, or epidemiological studies of the relation between asthma and occupation. The incidence, predominant causative agents, and jobs most commonly reported to incur risk depend on the methodology of data collection, case definition, and predominant work sectors and occupations. Studies generally do not distinguish between hypersensitivity and irritant causes. One systematic review showed an attributable risk of 9%, while the highest scoring studies showed an attributable risk of 15%, a figure supported by another review.

ES1*** SIGN 2++
Occupational factors are estimated to account for 9–15% of cases of asthma in adults of working age, including new onset or recurrent disease.

ES2*** SIGN 2++
The annual population incidence of occupationally related asthma ranges from an estimated 12–170 cases per million workers with an estimated mean of 47 cases per million workers.

ES3* SIGN 3
The population incidence of OA may be underestimated by as much as 50%.

ES4* SIGN 3
The reported incidence of OA has not decreased in recent years.

Table 1  Revised SIGN grading system for levels of evidence

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relation is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relation is causal</td>
</tr>
<tr>
<td>2</td>
<td>Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relation is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytical studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

ES5*** SIGN 2++
The most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes, and wood dust.

ES6*** SIGN 2++
The workers most commonly reported to surveillance schemes of OA include paint sprayers, bakers and pastry makers, nurses, chemical workers, animal handlers, welders, food processing workers, and timber workers.

ES7*** SIGN 2+
The workers reported from population studies to be at increased risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastics and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, waiters, cleaners, painters, plastic workers, dental workers, and laboratory technicians.

Four main risk factors have been identified for OA: the causative factor of exposure to an agent at work; the predisposing factors of atopy and genetic predisposition; and the contributing factor of cigarette smoking.

A direct relation between OA and exposure to an agent at work occurs with acid anhydrides, cimetidine, colophony, enzymes, green coffee and castor bean, flour allergens, crab, isocyanates, laboratory animal allergens, piperazine, platinum salts, prawns, and western red cedar. Most studies also showed a positive exposure-response relation for sensitisation. Studies limited to sensitisation showed a relation with exposure to acid anhydrides, enzymes, laboratory animals, and platinum salts.

ES8*** SIGN 2++
The risk of sensitisation and OA is increased by higher exposures to many workplace agents.
Differences in ascertaining atopy, from personal or family history of allergy to tests for specific immunoglobulin E (IgE), can cause inconsistencies between observations. Atopy is reported to increase the risk of OA in workers exposed to enzymes,34–36 isocyanates,44 laboratory and other animals,50–52 isocyanates,64 laboratory and other animals,66 125 and some reactive dyes.46 Other studies show no association between atopy and OA due to exposure to cork.31 isocyanates,48 66 127 enzymes,38 glutaraldehyde,54 salmon,54 crab,54 hexadrophthalic anhydride,54 platinum salts,54 68 and plicatic acid.54 Atopy is associated with increased risk of sensitisation in workers exposed to enzymes,34 50–52 65 66 68 69 112 green coffee and castor bean,50 54 bakery allergens,62–64 75 76 95 96 laboratory animals,54 crab,54 prawn,54 and acid anhydrides.37 54

ES9** SIGN 2++
Atopy increases the risk of developing OA caused by exposure to many high molecular weight (HMW) agents that induce the production of specific IgE antibodies.30 50–52 62 65 66–70

That only some workers develop OA despite similar exposures, suggests underlying genetic susceptibility. Studies have examined genetic predisposition to OA attributed to isocyanates,30–35 complex platinum salts,30 66–69 western red cedar,49 acid anhydrides,106 and laboratory animal proteins.54 109

Studies had small sample sizes and their findings were inconsistent or unreplicated.

ES10** SIGN 2–
Genetic polymorphisms that code for human leucocyte antigen (HLA) class II genes or respiratory antioxidant mechanisms may predispose to OA for a number of agents.70 85 101–103 127

Smoking increases the risk of OA in workers exposed to: isocyanates,45 54 66 101 platinum salts,54 90 111 salmon,66 and snow crab.46 Smoking increases the risk of sensitisation in studies with exposure to green coffee and castor bean,34 46 94 platinum salts,48 112 prawn,54 and flour.46 The role of smoking is unclear for OA due to other agents. Some studies show increased risk of laboratory animal asthma in smokers.50 79 112 whereas others show no effect.31 65 66 95 111 For acid anhydrides, studies show both negative31 and positive97 correlation with specific IgE. Conflicting evidence also exists for detergent enzymes.38 115 In bakery workers, one study showed an increased risk of sensitisation in smokers,46 but the risk of OA does not appear to be increased.46 75 95

ES11** SIGN 2+
Cigarette smoking can increase the risk of developing OA with some sensitising agents.46 54 58 63 76 80 111

Co-morbid rhinitis or rhino-conjunctivitis is reported in 45–90% of subjects suffering from IgE associated OA attributable to acid anhydrides,13 116 laboratory animals,29 30 46 66 snow crab,46 and wheat flour.46

ES12** SIGN 2+
Occupational rhinitis and OA frequently occur as co-morbid conditions in IgE associated OA.19 44 50 66 69 86 115–117

ES13** SIGN 2+
Rhino-conjunctivitis is more likely to appear before the onset of OA due to exposure to inhaled proteins.19 115

While the latent interval between first exposure and the onset of OA can extend to many years,19 116 117, risk is highest soon after first exposure to laboratory animal allergens,30 54 66 111 isocyanates,111 platinum salts,85 111 and azodicarbonamide.110

ES15** SIGN 2+
IgE sensitisation and OA are most likely to develop in the first years of exposure for workers exposed to azodicarbonamide, enzymes, complex platinum salts, isocyanates, and laboratory animal allergens.50 52 54 68 69 86 111 112 122 123

Prevention
With any study of preventive measures, it is difficult to distinguish the relative effect of one measure against another, since they are usually implemented as a composite programme. Studies show that reducing exposure leads to fewer cases of OA from acid anhydrides,13 126 detergent enzymes,38 39 isocyanates,99 laboratory animals,126 and latex.126

ES16** SIGN 2+
Reducing airborne exposure reduces the number of workers who become sensitised and who develop OA.11 50 66 68 86 125–129

Table 2  Revised SIGN grading system for recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Source of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1++, directly applicable to the target population, and showing overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+</td>
<td></td>
</tr>
<tr>
<td>B A body of evidence including studies rated as 2++, directly applicable to the target population, and showing overall consistency of results, or extrapolated evidence from studies rated as 2++</td>
<td></td>
</tr>
<tr>
<td>C A body of evidence including studies rated as 2+, directly applicable to the target population and showing overall consistency of results, or extrapolated evidence from studies rated as 2+</td>
<td></td>
</tr>
<tr>
<td>D Evidence level 3 or 4, or extrapolated evidence from studies rated as 2+</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Modified RCGP three star system

<table>
<thead>
<tr>
<th>Source of evidence</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong evidence</td>
<td>***</td>
</tr>
<tr>
<td>Moderate evidence</td>
<td>**</td>
</tr>
<tr>
<td>Limited or contradictory evidence</td>
<td>*</td>
</tr>
<tr>
<td>No scientific evidence</td>
<td>No rating</td>
</tr>
</tbody>
</table>

www.occenvmed.com
Respiratory protective equipment (RPE) only offers protection when worn properly, removed safely, and either replaced or maintained regularly. Studies are few and small; one observed a significant association between symptoms and even brief removal of RPE.\(^{14}\)

**ES17** SIGN 3

The use of RPE reduces the incidence of, but does not completely prevent, OA.\(^{33 149}\)

Pre-placement examinations should be used to establish a baseline for periodic health surveillance rather than to detect and exclude susceptible individuals from workplaces. Little is known about host susceptibility factors, except for atopy in those exposed predominantly to high molecular weight agents. The efficiency of screening out susceptible job applicants depends partly on the frequency of the trait in the general population.

**ES18** SIGN 3

The positive predictive values of screening criteria are too poorly discriminating for screening out potentially susceptible individuals, particularly in the case of atopy where the trait is highly prevalent.\(^{77 112 121 130 132}\)

**ES19** SIGN 3

A previous history of asthma is not significantly associated with OA.\(^{36 66}\)

Periodic health surveillance aims to identify sensitised workers or cases of OA at early and reversible stages of disease. There are few, and no concurrent comparison studies of the efficacy of health surveillance for OA. The only study from which valid conclusions can be drawn is of isocyanate workers, in whom health surveillance was linked to a mandatory programme of control of exposure. Workers with isocyanate induced asthma were diagnosed sooner after symptoms began, had better lung function and better outcome than workers who had asthma attributable to other workplace agents\(^{113}\) although the results might partly be attributable to concomitant reduction in exposure. Few studies have evaluated the separate components of health surveillance, questionnaires, spirometry, and identification of specific IgE. In one, all true cases of OA were identified by questionnaire, spirometry producing many false positives due to poor inspiratory effort and no additional cases of asthma.\(^{144}\) In another, spirometry detected one case of OA in addition to two cases identified by questionnaire.\(^{145}\) Skin prick and serological tests can detect specific IgE in workers who have become sensitised to HMW agents and a few low molecular weight (LMW) agents (complex platinum salts, acid anhydrides, and some reactive dyes).

**ES20** SIGN 3

Health surveillance can detect OA at an earlier stage of disease and outcome is improved in workers who are included in a health surveillance programme.\(^{146}\)

**ES21** SIGN 3

Screening questionnaires may lead to an underestimate of the prevalence of asthmatic symptoms.\(^{136 137}\)

**ES22** SIGN 3

Spirometry detects few cases of OA that would not otherwise be detected by respiratory questionnaire.\(^{146 147}\)

**ES23** SIGN 2+

Skin prick testing and blood sampling of exposed workers to conduct immunological tests is feasible in the workplace.\(^{148 149}\)

**ES24** SIGN 2+

Prospective surveillance for the development of specific IgE antibodies can be used as part of a broader risk management programme to reduce the incidence of OA.\(^{150 151}\)

Identification and evaluation of OA

Most evidence relating to the diagnosis of OA emanates from specialist settings where the prior probability of disease and positive predictive values of tests may be high. History alone produces false positive diagnoses, requiring further validation. Serial measurement of peak expiratory flow (PEF) is the simplest initial investigation. When performed and interpreted to validated standards there are few false positive results, but about 20% false negatives. Skin prick or blood tests for specific IgE are available for most HMW agents and a few LMW agents but few standardised allergens are commercially available. OA can usually be diagnosed without specific bronchial provocation testing (SBPT).

The symptoms of any type of asthma have high sensitivity but lower specificity, whereas the question “have you been told by a doctor that you have asthma” has a higher specificity but lower sensitivity.\(^{147}\) Asking about deterioration at work is an insensitive method of diagnosing OA. Questioning about symptoms that are better on days away from work has a sensitivity of 58–100% for validated OA and is enhanced by asking about symptoms improving on holiday. Work related symptoms are common in those with negative SBPT.

**ES25** SIGN 2+

In the clinical setting questionnaires that identify symptoms of wheeze and/or shortness of breath that improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for OA.\(^{138 139 140 141}\)

**ES26** SIGN 3

Free histories taken by experts have high sensitivity, but their specificity may be lower.\(^{152 153}\)

No good studies compare cross-shift changes with SBPT. Such testing is unlikely to be either sensitive or specific since measures of airflow obstruction show diurnal variation in most normal workers that is increased in most asthmatics. In one study a fall in FEV\(_1\) of >10% post-shift was found in 5% of asymptomatic workers and 32% of those with work related asthma symptoms.

**ES27** SIGN 3

Pre-to-post-shift changes in lung function cannot be recommended for the validation or exclusion of OA.\(^{154 155}\)

Serial PEF was studied in small case series of patients attending specialist clinics or workplace surveys. Over 70% of subjects in four clinical series and each of the workforce populations returned acceptable records. A single case series of 74 patients attending a specialist clinic reports the highest combination of sensitivity and specificity with PEF measured at least four times daily. Less frequent readings produced higher specificity but lower sensitivity. Six series report high levels of agreement (averaging 80%) between expert assessors. A single series, using non-expert assessors, reports much lower inter-observer agreement. Eight case series report direct and blinded comparisons of serial PEF measurement and either SBPT or an expert diagnosis based on a combination of other evidence. Sensitivities and specificities were consistently high, averaging 80% and 90% respectively. Three case series compare visual inspection of PEF records by experts with a variety of statistical indices. One computed analysis reported sensitivity of 75% and specificity of 94%.
when analysis was calibrated using the opinion of one expert in cases whose OA was mostly attributable to LMW agents.

**ES28** **SIGN 3**

Acceptable PEF series can be obtained in around two thirds of those in whom a diagnosis of OA is being considered.156 157 159 164 166

**ES29** **SIGN 3**

The diagnostic performance of serial PEF measurements falls when fewer than four readings a day are made.159

**ES30** **SIGN 3**

There is high level of agreement between expert interpretations of serial PEF records.155 159 160 161–164

**ES31** **SIGN 3**

The sensitivity and specificity of serial PEF measurements are high in the diagnosis of OA.146 147 153 159 162 164–166

**ES32** **SIGN 3**

Statistical analysis of serial PEF measurements is of limited diagnostic value compared to expert interpretation.147 155 156

**ES33** **SIGN 2+**

Computed analysis of PEF records has good diagnostic performance.160 167

Many studies show that non-specific bronchial hyper-reactivity is normal in 5–40% of SBPT positive workers. Testing with higher concentrations of methacholine or histamine at which some non-asthmatics react reduces the number of, but still leaves some, non-reacting asthmatics. A normal test of non-specific reactivity is not sufficiently specific to exclude OA.

**ES34** **SIGN 2++**

A large number of concordant studies from different centres using different methodologies showed that increased non-specific reactivity is often found in workers with OA. There are however many reports of normal methacholine or histamine reactivity within 24 hours of exposure in workers with confirmed OA.142–145 149 150 156 164 166–177

**ES35** **SIGN 2−**

Changes in non-specific reactivity at and away from work alone have only moderate sensitivity and specificity for diagnosis.160 162 177

**ES36** **SIGN 3**

Paired measurements of non-specific reactivity may be achieved in the workplace.177 179

The sensitivities and specificities of skin prick or serological tests to detect specific IgE vary between allergens and with positive cut-off levels. Serological tests may not be as sensitive as skin prick testing.179 The presence of specific IgE confirms sensitisation to an agent at work, but alone does not confirm OA, or necessarily its cause. There is a high false positive rate although, with HMW agents, few false negatives. Specific IgE is an insensitive but specific test for isocyanate induced OA,180 although this may depend on the time since last exposure. A small study reported greater sensitivity for MDI (83%) than TDI (27%).181

**ES37** **SIGN 2+**

Both skin prick and serological tests are highly sensitive for detecting specific IgE and OA caused by most HMW agents, but are not specific for diagnosing OA.182 183

**ES38** **SIGN 2+**

Both skin prick and serological tests are sensitive for detecting specific IgE and OA caused by acid anhydrides and some reactive dyes, but have a lower specificity for diagnosing OA.179 184 185

**ES39** **SIGN 2+**

Skin prick tests are highly sensitive but less specific for OA caused by complex platinum salts.159 170 175

SBPT is used as the gold standard for OA diagnosis, making assessments of its diagnostic validity difficult. Standardised methods are lacking for many occupational agents. The threshold exposure increases with time since last exposure, making tests less sensitive after prolonged absence from work. Individuals can have non-specific reactions to SBPT at concentrations likely to be found in the workplace and negative SBPT with otherwise good evidence of OA when challenge concentrations are below occupational exposure standards.151 152 170 175 176

**ES40** **SIGN 4**

Carefully controlled specific challenges come closest to a gold standard test for some agents causing OA.

**ES41** **SIGN 4**

A negative test in a worker with otherwise good evidence of OA is not sufficient to exclude the diagnosis.

**Management of the worker with OA**

The outcome of interventions following a confirmed diagnosis of OA may depend on several factors, including the worker’s age and the causative agent. Early diagnosis and avoidance of further exposure, either by relocation of the worker or substitution of the hazard, offer the best chance of complete recovery. If these are impossible, workers should be relocated to low or occasional exposure areas and have increased health surveillance. Studies investigating the effectiveness of RPE in those with OA are limited to small studies in provocation chambers or limited case reports. The risk of unemployment may or may not be higher in other adult asthmatics and may fall with increasing time from diagnosis.186 187 No studies make direct comparisons between different systems of rehabilitation. There is one small RCT of the effect of inhaled corticosteroids on recovery from OA after ceasing exposure.

**ES42** **SIGN 2+**

The symptoms and functional impairment of OA caused by various agents may persist for many years after avoidance of further exposure to the causative agent.188 189 190–209

**ES43** **SIGN 2++**

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent.190 204 205 210–216

**ES44** **SIGN 2+**

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have relatively normal lung function at the time of diagnosis.195 196 201 202 209 210 217 218

**ES45** **SIGN 2+**

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to diagnosis.190 199 204–206 215 218 219
The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to avoidance of exposure.107 108 109 110

Redeployment to a low exposure area may lead to improvement or resolution of symptoms or prevent deterioration in some workers, but is not always effective.111 112 113 114

Air fed helmet respirators may improve or prevent symptoms in some but not all workers who continue to be exposed to the causative agent.115 116 117 118

Approximately one third of workers with OA are unemployed up to six years after diagnosis.119 120 121 122 123

Workers with OA suffer financially.124 125 126 127 128 129

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