

ONLINE SUPPLEMENT

Appendix A

Evidence Review Update

EVIDENCE REVIEW UPDATE

BOHRF methodology is described in the 2004 and 2010 systematic reviews.[1,2] Studies addressing research questions were identified using MEDLINE and EMBASE, selected papers being critically appraised and graded using the modified Royal College of General Practitioners (RCGP) system and the Scottish Intercollegiate Guidelines Network (SIGN) system.

Updated evidence is discussed sequentially in the domains; (A) background, (B) prevention, (C) identification and evaluation of OA in a symptomatic worker and (D) management of the worker confirmed to have OA.

A. Background;

A1; BOHRF 2010 states “Occupational factors are estimated to account for 1 in 6 cases of adult asthma”. This alters the original similar estimate of 15% of adult asthma, based on new evidence from Toren *et al* (2009).[3] The level of evidence for this statement is upgraded from ***SIGN 2++ to ***SIGN 1++.

A2; the incidence for cases of OA has been upwardly revised to between 12 and 300 cases/workers/year, based on new data, including from Bakerly *et al*,[4] Kogevinas *et al*,[5] McDonald *et al* [6] and Orriols *et al*. [7]

A3; The evidence rating for the statement “the incidence of OA identified by reporting schemes may be significantly underestimated” has increased to *SIGN 2+ from *SIGN 3, supported by data [7] identifying that the number of cases reported to a voluntary surveillance system were four fold that reported by the compulsory official system.

A4; most frequently reported agents causing OA are expanded to include adhesives, metals, resins in addition to isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes, and wood dust.

A5; hairdressers are added to the list of workers most commonly reported to reporting schemes with OA.

A6; added to the list of workers reported from population studies are cooks, healthcare workers, woodworkers and mechanics.

A12; the 2010 review states that rhinoconjunctivitis may precede or coincide with the onset of OA, now emphasising that rhinoconjunctivitis may not always precede the onset of OA.

A13; the statement “the risk of developing OA is highest in the year after the onset of occupational rhinitis” remains unchanged, but has a stronger evidence rating (***SIGN 2++) based on cohort and cross-sectional studies [8-10] not included earlier.

B. Prevention of OA;

B4; new data from a large study of workers with possible OA identified by health surveillance [11] further supports the usefulness of health surveillance for detecting OA early.

B6; added comment supports the earlier view that screening questionnaires used for case-finding generally underestimate the presence of OA. The strength of evidence is upgraded (**SIGN 2++), based on a study comparing results from a cohort of workers to a cross-sectional survey.[12] This noted significant disparity between possible OA identified by “in-

house" health surveillance and a research project in bakeries.

B7; new evidence supports the statement that spirometry detects few cases of OA that would not otherwise be detected by respiratory questionnaire. The level of evidence was strengthened to **SIGN 2+ [from *SIGN 3] after re-evaluating the original study designs (cohort and cross-sectional studies).

C. Identification and evaluation of a case of OA in the worker presenting with respiratory symptoms;

C3; pre to post shift changes in lung function are again assigned a relatively low strength evidence for the statement that suggests that these tests have high specificity but only low sensitivity for a diagnosis of OA. Further data [13] are cited, assessing mean peak expiratory flow (PEF) changes across morning and day shifts and compared these between workers with OA confirmed using specific challenge testing and non-working asthma patients. Serial analysis using mean work-rest day PEF comparison had a sensitivity of 66.7% and a specificity of 100% for making a diagnosis of OA, whilst cross-shift changes in PEF in morning / day-shift workers had a poor sensitivity.

Substantial evidence supports the use of serial PEF measures as a useful investigation for occupational asthma. [14-20]

C4; the statement regarding the ability to obtain acceptable PEF readings is strengthened to ***SIGN 2++ [from **SIGN 3] adding "in specialist settings". Recent evidence suggests that specialist clinics are superior in obtaining good quality PEF data compared to "other health units". Sauni *et al* [21] assessed quality of diagnostic procedures, reviewing case notes of 150 patients referred to the Finnish Institute of Occupational Health with a suspected occupational cause of their asthma. Workplace measurements of serial PEF were performed in 51% of all cases; quality of measurements being "sufficient" in 52%. Serial PEF measurements were performed significantly ($p < 0.01$) less often in other health clinics (23%) compared to occupational health (56%) or respiratory clinics (59%).

C5; the statement that the diagnostic performance of serial PEF measurements taken to investigate potential OA falls when fewer than 4 readings a day are taken is modified, adding "when records are shorter than three weeks in duration", based on a case series. The evidence rating remains unaltered.[22]

C6; minor alteration is made to the evidence statement regarding expert agreement when interpreting serial PEF, the new statement noting *SIGN 3 evidence for moderate agreement between experts.

C7; evidence relating to high sensitivity and specificity of serial PEF for a diagnosis of OA is strengthened to ***SIGN 1++, additional comment emphasising that these are quality dependent.

C8; this newly worded statement is assigned a reduced strength of evidence [*SIGN 3], noting "computer-based analyses of peak flow records may be helpful in the diagnosis of OA".

Assessment of non specific bronchial responsiveness (NSBR) may assist making a diagnosis of occupational asthma.[23]

C9; the section discussing single measurements of NSBR is expanded to include pooled estimates of sensitivity and specificity using specific bronchial provocation tests (SBP) as the reference standard.[24] Evidence statement C9 notes that a single measurement of non-specific reactivity has only moderate specificity and sensitivity for the validation of OA and is graded ***SIGN 1++.

C10; regarding temporal changes in NSBR, this statement notes: "changes in NSBR at and away from work alone have only moderate sensitivity and specificity for diagnosis (of OA) and

was downgraded to *SIGN 3 after re-evaluating studies, all being case series. The evidence that these measures are achievable remains unchanged (statement c11; *SIGN 3).

C12; A meta-analysis provided pooled estimates [24] of sensitivities and specificities of specific skin prick tests and serum specific IgE compared to SPBT. The two evidence statements are strengthened as follows; c12; both skin prick and serological tests are sensitive for detecting specific IgE and OA caused by most high molecular weight agents but are not specific for diagnosing asthma [*** SIGN1++] and; c13; overall, both skin prick and serological tests are less sensitive for detecting specific IgE and OA caused by low molecular weight agents and while specificity may be higher they are not specific for diagnosing asthma *** SIGN1++.

Specific challenge testing [25-27] and workplace challenge testing [28] remain important investigations for occupational asthma.

The 2010 review is expanded to include newer diagnostic modalities of exhaled nitric oxide (FeNO) and sputum eosinophilia, there being little evidence for these tests previously.

C15 states: "the role of FeNO measurements in the diagnosis of OA is not established" *SIGN 3.

C16 concludes: "In the clinical setting a normal FeNO does not exclude a diagnosis of OA", *SIGN3.

Two evidence statements are included on the utility of sputum eosinophilia for the diagnosis of OA: both are graded *SIGN 3. These are C17 - the measurement of sputum eosinophils may be helpful in the diagnosis of OA and C18 - in the clinical setting the absence of sputum eosinophilia does not exclude a diagnosis of OA. Both statements were based on a recent studies including a meta analysis.[24]

D. Management principles for the worker confirmed to have OA

The inclusion of a meta-analysis [29] upgraded the evidence to *** SIGN 1++ for the statement D1; The symptoms and functional impairment of OA may persist for many years after avoidance of further exposure to the causative agent.

A new statement is included regarding the utility of reducing exposure; D7 [** SIGN 2+], although based solely on evidence related to exposure to natural rubber latex gloves.[30] Where clinical considerations permit, reduction of exposure may be a useful alternative associated with fewer socio-economic consequences to complete removal from exposure.

A new evidence statement D13, based in part on data from Fishwick *et al* [31] discusses referral delays, concluding: "lengthy diagnostic delay occurs for patients with OA" ** SIGN 3.

OCCUPATIONAL ASTHMA
Table 1
Summary of major BOHRF recommendations for health practitioners

- * **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.
- ** **SIGN 2+**; The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have little or no further exposure to the causative agent.
- ** **SIGN 2+**; Occupational rhinitis and OA frequently occur as co-morbid conditions.
- ** **SIGN 2+**; Rhinoconjunctivitis is more likely to appear before the onset of IgE associated OA.
- *** **SIGN 2++**; The risk of developing OA is highest in the year after the onset of occupational rhinitis.
- *** **SIGN 1++**; Occupational factors are estimated to account for about 1 in 6 cases of asthma in adults of working age, including new onset or recurrent disease.
- *** **SIGN 2++**; The workers most commonly reported to surveillance schemes of OA include animal handlers, bakers and pastry makers, chemical workers, food processing workers, hairdressers, paint sprayers, nurses and other health professionals, timber workers and welders.
- ** **SIGN 2+**; The workers reported from population studies to be at increased risk of developing asthma include bakers, chemical workers, cleaners, cooks, electrical and electronic production workers, farm workers, food processors, forestry workers, healthcare workers, laboratory technicians, mechanics, metal workers, painters, plastics and rubber workers, storage workers, textile workers, waiters, welders and wood workers.
- *** **SIGN 2++**; The most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.
- ** **SIGN 2+**; In the clinical setting questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for the validation of OA.
- ** **SIGN 2+**; In the clinical setting questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for the validation of OA.
- * **SIGN 3**; Free histories taken by experts have high sensitivity, but their specificity may be lower. These values may be affected by differences in language and populations.
- ** **SIGN 2+**; Approximately one third of workers with OA are unemployed up to 6 years after diagnosis.
- ** **SIGN 2+**; Workers with OA suffer financially.
- ** **SIGN 3**; In specialist settings acceptable peak flow series can be obtained in around two thirds of those in whom a diagnosis of OA is being considered.
- * **SIGN 3**; The diagnostic performance of serial peak flow measurements falls when fewer than four readings a day are made and records are shorter than three weeks.
- ** **SIGN 3**; There is high level of agreement between expert interpretations of serial peak flow records.
- ** **SIGN 3**; Depending on the quality of the recorded series, the sensitivity and specificity of serial peak flow measurements are high in the diagnosis of OA.

Table 2
Common agents and jobs related to OA

Source	Agent or job
Most commonly reported agents causing OA;	Isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes, adhesives, metals, resins and wood dust
Workers most commonly reported to surveillance schemes of OA include;	Animal handlers, bakers and pastry makers, chemical workers, food processing workers, hairdressers, paint sprayers, nurses and other health professionals, timber workers and welders
Workers reported from population studies to be at increased risk of developing asthma include;	Bakers, chemical workers, cleaners, cooks, electrical and electronic production workers, farm workers, food processors, forestry workers, healthcare workers, laboratory technicians, mechanics, metal workers, painters, plastics and rubber workers, storage workers, textile workers, waiters, welders and wood workers.

Overall Case Management

Ideally, affected workers should be redeployed within the same workplace, in a non-exposed task, in order to minimise the consequences discussed below. In practice, this may not happen, and workers may remain exposed, or have their employment terminated. Where clinical considerations permit, reduction of exposure may be an acceptable alternative to complete removal from exposure, associated with fewer socio-economic consequences. Continued follow-up is essential in this situation to ensure symptoms and exposures are reduced and that lung function preserved. The use of software to assess individual (or group) FEV₁ decline with time (e.g. Spirola, TM, NIOSH, web address; <http://www.cdc.gov/niosh/topics/spirometry/spirola.html> last accessed 04.07.2011) is recommended.

Patients with OA should be told of the possibilities for compensation. Local context will alter regulations for compensation, e.g. in Great Britain they should be advised where appropriate about Industrial Injuries Disease Benefit and helped with this if necessary. More information can be found at; www.dwp.gov.uk/advisers/claimforms/ (last accessed 04.07.2011).

Patients should be advised about a potential civil claim where appropriate. In particular, patients should be told that if a civil claim is anticipated, a time limit might apply following the date of knowledge (the date the individual became aware that their asthma was occupational in origin) may apply beyond which it is not possible to commence a claim. This time period is usually 3 years in England. There are regional UK differences in Civil Law, and it is appropriate to tell patients to take advice from a personal injury lawyer, if they are contemplating legal action.

The Equality Act 2010 protects the rights of workers with various forms of disability. The legislation protects a disabled person thought to be at a "substantial disadvantage in comparison with persons who are not disabled". This means that employers have to make one or more reasonable adjustments for those satisfying the definition of disability by virtue of having asthma, whatever the cause.

Audit tool

The audit tool, against which clinical activity should be measured, is revised as follows. All patients with suspected OA should, as a minimum, have the following clearly documented in their health records.

By first visit

- Presence or absence of asthma prior to potentially harmful asthagen exposure at work
- Presence or absence of work-related eye or nasal symptoms
- Presence or absence of work-related respiratory symptoms and their duration
- A full list of occupations held, their durations, and likely associated occupational exposures
- Current ongoing asthagen exposure
- Whether other workers at the same workplace are affected
- FEV₁, FVC, and the degree of airflow limitation, compared to predicted values

By second visit

- If at work and appropriate; serial PEF measurements taken for at least 3 continuous weeks including rest days, with at least 4 good quality readings per day, analysed to assess work relatedness.
- If performed, the results of non specific bronchial responsiveness

- If exposed to allergen with appropriate specific IgE measure or skin prick test, the result of this test.

Once a diagnosis of OA is confirmed

- Letter to patient concerning advice about continuing employment
- Compensation advice (IIDB and civil action) where appropriate to the case

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