Recent developments in occupational asthma

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Summary

Occupational exposures now account for 20% of adult onset asthma. Overall incidence has not declined, but recognition of the problem and substitutions have resulted in dramatic reductions in some causes of occupational asthma, particularly latex and glutaraldehyde in healthcare workers. Newer at risk workers include cleaners and those exposed to metal-working fluid. Standards of care have now been published, supported by evidence-based reviews of the literature, which are likely to require referral to centres specialising in occupational asthma for compliance. The spectrum of occupational asthma is expanding, with low-dose irritant mechanisms likely to account for some occupational asthma with latency. Eosinophilic and non-eosinophilic phenotypes are also seen, the non-eosinophilic variant having more normal non-specific responsiveness than the eosinophilic subgroup. Physiological confirmation of occupational asthma is required but remains challenging. Specific challenges may be negative in workers confirmed as having occupational asthma from workplace challenges. Serial measurements of peak expiratory flow or FEV₁ are feasible in the occupational health and general respiratory clinic settings and provide a method of validation of occupational asthma in those without ready access to specific challenge testing, while minimum data quantity standards are now established which need to be achieved for optimal sensitivity/specificity. New developments in the analysis of serial measurements of peak expiratory flow comparing the mean hourly values on work and rest days have shown good specificity and sensitivity from shorter records (but more frequent readings) than needed for the standard Oasys score.

Key words: occupational asthma; Oasys; bronchial responsiveness; peak expiratory flow; low-dose irritant athlete; skier; induced sputum; diagnosis; review

Guidelines

Several guidelines have recently been published, two of which have involved a systematic search of literature. In 2005 the British Occupational Health Research Foundation (BOHRF) produced evidence-based guidelines for occupational asthma [1] and in 2007 a systematic review was conducted of diagnostic methods, mainly comparing the results of measures of specific IgE and non-specific bronchial responsiveness with specific challenge testing and calculating pooled sensitivities and specificities [2]. Both sets of guidelines produced similar results and in particular demonstrated that there are workers with current exposure with non-specific reactivity measurements within the normal range, the meta-analysis showing a mean value of 20% to have normal non-specific reactivity measurements with confidence intervals between 12 and 32%. A normal non-specific reactivity measurement can therefore not be used as an exclusion criterion for the further investigation of occupational asthma.

The British Thoracic Society has produced standards of care for occupational asthma based on the BOHRF guidelines and provided an audit tool giving a list of items that should be documented in the notes by the second consultation, as follows [3]:
1. A full list of occupations held and likely associated occupational exposures
2. FEV₁/FVC
3. Serial peak expiratory flow with at least four readings a day and at least four continuous weeks, including rest days, analysed by a valid method (if at work)
4. Skin prick testing or specific IgE for appropriate antigens
5. A letter to the patient concerning advice about continuing employment once a diagnosis has been made
6. Appropriate compensation advice

Standards of this sort are likely to need specific clinics for occupational respiratory diseases, since at least in the UK the resources and expertise available fall far short of these standards [4].

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Incidence of occupational asthma

Overall there is no evidence that occupational asthma is becoming less frequent. The proportion of adult onset asthma due to occupational factors has been revised upwards over the last 40 years from less than 5% to a figure now of around 20% [5], which will include both irritant and allergic occupational asthma. It is hard to think of any other common cause of adult onset asthma. This makes a search for occupational asthma in every adult with airflow obstruction appropriate. The best screening questions are to ask whether the worker is better on days off work or on holiday and, if they are, further investigation is needed. Occupational asthma can be confirmed in about half of patients responding affirmatively to these questions [6]. There have been some notable successes in reducing occupational asthma, especially from latex and glutaraldehyde in health care workers [7]. The substitution of latex gloves with vinyl or nitrile gloves and the removal of glutaraldehyde from most sterilising agents has largely eliminated these two causes of occupational asthma in medical facilities which have substituted them for safer materials. On the other hand, there have been no substantial reductions in the number of baker’s asthma worldwide, where it is estimated that exposure levels will need to come down around 10-fold to have a significant impact on sensitisation to flour and enzymes [8–10]. The situation with isocyanate asthma is more complicated, as various attempts at substitution, initially from toluene di-isocyanate to diphenylmethane di-isocyanate and more latterly to poly-isocyanates, has not resulted in any reported reduction in isocyanate asthma worldwide [11]. The number of agents causing occupational asthma is increasing but the major causes remain the same – particularly flour, wheat, isocyanates, solder fluxes, wood dusts and, more recently, cleaning agents and metal-working fluids [1, 7].

Can low-dose irritation cause occupational asthma with latency?

Acute irritant-induced asthma is now well established where a normal individual has overwhelming exposure to a known irritant, develops asthma within 24 hours, and where the asthma persists for more than three months after the incident [12]. The asthma that develops is similar to non-occupational asthma and sensitisation has not occurred, with the result that low-level exposure to the same agent is usually tolerated without problems. Chlorine exposure is the most common cause but a wide range of chemicals and fires have been implicated.

There is increasing evidence that low-level exposure to an irritant can result in asthma that deteriorates with low-level exposure and improves afterwards, and this is associated with latency in a similar manner to sensitisation-induced asthma. Once developed it is difficult to separate from occupational asthma due to sensitisation. There are a large number of agents which have been thought to act as primary irritants; however, when latency exists it is very difficult to know whether the mechanism is via an allergic or irritant mechanism. This particularly applies to situations such as aluminium foundries where the fluoride and hydrochloric acid in the air are recognised irritants but where only a minority of individuals develop work related asthma after a latent period, and it is also possible that this is due to sensitisation to the aluminium fluoride salts [13, 14]. Aluminium chloride has been shown to be a cause of occupational asthma due to sensitisation, supporting this hypothesis [15].

There is much recent interest in elite athletes, many of whom have developed asthma during training. This particularly applies to elite swimmers; their exposures are complicated by nitrogen trichloride in the air above the water in swimming pools. Nitrogen trichloride has also been demonstrated to be a cause of occupational asthma [16]. Ice hockey players have also shown more asthma and non-specific bronchial responsiveness than handball players [17], but may also be exposed to diesel exhaust from ice resurfacers, another possible cause of low-dose irritant induced asthma [18].

The least confounded cause of low-dose irritant induced asthma is from cold air: there have been studies in elite cross-country skiers demonstrating new onset asthma in a substantial proportion of skiers who are exposed to unpolluted cold air; this is often associated with new onset non-specific bronchial reactivity [19]. Bronchial biopsies have shown histological changes with basement membrane thickening and some increase in T-lymphocytes, macrophages and eosinophils compared with non-asthmatic controls, but usually to a somewhat lesser extent than with non-occupational asthmatics [19].

Irritant-induced contact dermatitis is well established, where repeated low-level insults to the dermis result in dermatitis which looks very similar to allergic contact dermatitis. Patch testing however shows a sharp concentration threshold and reactions in non-exposed individuals, separating allergic from irritant mechanisms. Unfortunately there is no differential test, such as the patch test, available for asthma. At present we don’t know whether the prognosis is any better for low-dose irritant-induced asthma than it is for allergic asthma, but in elite athletes the asthma may well persist after training ceases, suggesting that low-dose irritant-induced asthma is not necessar-
ily a benign condition [20]. If the athlete is a professional, this is presumably a variety of occupational asthma [17].

**Eosinophilic and non-eosinophilic occupational asthma with sensitisation**

Non-specific bronchial reactivity is a feature of most asthmatics, and has been used by some to screen workers for further investigation for occupational asthma. Hyperresponsiveness may be transient and return to normal with avoidance of exposure, and so needs to be measured within 24 hours of last exposure. Studies where this has been done report a proportion with normal non-specific bronchial reactivity and otherwise good evidence of occupational asthma [1, 21]. The recognition that occupational asthma may exist without non-specific bronchial reactivity has led to a search for different phenotypes of occupational asthma. Induced sputum has been used as a marker of eosinophilic bronchial inflammation and is present in the majority, but not all, of those with non-occupational asthma [21]. However, in the occupational setting there are a substantial proportion of subjects with occupational asthma without sputum eosinophilia. One study of low molecular weight asthma showed that only the minority had sputum eosinophilia, that the sputum eosinophilia correlated with exhaled breath nitric oxide (as in other populations) and that the group without sputum eosinophilia had less non-specific reactivity and less bronchodilator reversibility than the eosinophilic group. However, they were exposed to the same agents, had the same latent intervals and had the same degree of reaction in the workplace as the eosinophilic group [21]. Hence there seem to be at least two phenotypes of occupational asthma with latency. The lack of sputum eosinophilia or a normal exhaled breath nitric oxide does not exclude an individual from the diagnosis of occupational asthma.

**Validation of a diagnosis of occupational asthma**

It is generally agreed that specific bronchial dilatation testing is the gold standard. However, it is neither feasible nor available for many workers with occupational asthma. A recent study has looked at individuals with a good history of occupational asthma and negative specific challenge testing, and showed that 29 of 99 workers had a positive workplace challenge after a negative specific challenge, and of the 70 who had no asthma following a workplace challenge both asthma and rhinitis were excluded in 34. In 29/65 asthmatics with a good history of workplace deterioration occupational asthma was therefore confirmed despite a negative specific challenge [22]. This has led to a resurgence in alternative methods for diagnosis. The sensitivity and specificity of different physiological tests for occupational asthma are shown in table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial peak flow records (Oasys score) ≥4 per day and ≥3 weeks [23]</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>Serial peak flow (Oasys score) with &lt;4 per day and &lt;3 weeks [23]</td>
<td>64</td>
<td>83</td>
</tr>
<tr>
<td>Serial peak flow ABC score &gt;15 L/min per hour [24]</td>
<td>71</td>
<td>92</td>
</tr>
<tr>
<td>ΔPEF &gt;5L/min pre/post day shift [25]</td>
<td>50</td>
<td>91</td>
</tr>
<tr>
<td>3.2 x change in non-specific reactivity [26]</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td>Workplace challenge Unknown</td>
<td></td>
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<tr>
<td>Specific challenge [22] Unknown but &lt;100%</td>
<td>Unknown but &lt;100%</td>
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**Developments in the analysis of serial FEV₁ or peak flow measurements at work**

Logging meters have allowed the collection of FEV₁ and peak flow readings from the same exhalation in the workplace. Current evidence suggests that either are applicable to the diagnosis of occupational asthma and the percentage changes in FEV₁ are similar to the percentage changes in peak flow [27], but individual meters differ in their ability to record these accurately.

The original computer-assisted analysis of serial peak flow records required at least four readings a day, at least three periods off work and three periods at work (the periods at work lasting at least
both [30]. Analysis of the area between the curve (ABC score) has shown good sensitivity and specificity, if plotted from waking time [24].

An extension to this method has been developed looking at the 95% confidence intervals for the pooled standard deviations for the readings on rest days, and looking at individual mean values on workdays which show values below the 95% confidence interval for rest days. If there are two time points with significant deteriorations on workdays occupational asthma is likely [31]. Both these methods require readings of shorter duration but do benefit from 2-hourly rather than 4 times daily readings. Four or more recordings per day are achievable in >90% even after postal instruction [32], more easily achievable than the other minimum quantity criteria for the Oasys score. The 2-hourly standard does not need to be strictly by clock time but can be waking, arriving at work, during each rest break at work, on leaving work, midevening and on going to bed, with similar times on days away from work. The main reason that the analysis of time points is not feasible is that the recording times are different on workdays and on rest days, particularly due to later waking on rest days. The time point analysis does show that very small changes in peak flow are sometimes compatible with a diagnosis of occupational asthma confirmed by specific challenge testing, similar to the findings with this method initially developed for detection of late asthmatic reactions following specific challenge testing [33]. The time point analysis is also appropriate for the analysis of workplace challenges, although it has not been formally evaluated against independent diagnostic methods in this situation.

Figure 1
Oasys plot of 2-hourly PEF in a plastic moulder sensitised to formaldehyde. The middle panel shows the daily maximum (upper dotted line), mean (middle solid bars) and minimum (lower dotted line). Days at work have a shaded background, days away from work a clear background. The PEF is low (predicted 537, top dotted line), the Oasys discriminant analysis score is 3.14 (scores over 2.5 are significant), but the changes are relatively small.

Figure 2
Plot of mean 2-hourly PEF expressed as hours from waking from the same record in the plastic moulder shown in fig. 1. The top line shows the mean PEF on days away from work and the lower line the mean values for workdays. The shaded areas show the times worked, the darker section shows the modal time of starting and stopping work, the paler area the earliest time of starting work. Below the times are the numbers of readings contributing to each timepoint, and below that the mean difference between the work and rest day value for each period. The ABC score (Area Between Curves) is 33 L/min/hour. Values over 15 L/min/hour indicate occupational asthma. The circled work timepoints show those outside the 95% confidence intervals for days away from work. 6/9 are positive, if >1 is positive occupational asthma is likely. All three scores in this worker show an occupational effect, giving a specificity of 100% and a sensitivity of 56%. If only one of the three measures was positive the sensitivity would be 89% and specificity 80%. He had a positive specific challenge test to formaldehyde.
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Resources

The website www.occupationalasthma.com provides support for the analysis of serial PEF measurements in the diagnosis of occupational asthma, has a comprehensive list of references for occupational asthma, provides help for workers and medics through forums, and is freely available to all [34]. If one publishes work related to occupational asthma one can have one's own web page over which one has control.

References


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