Occupational asthma: a review of current concept

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Introduction

Occupational asthma (OA) presents a major health challenge with significant potential for acute morbidity, long-term disability, and adverse social and economic impacts.[1] It is one of the commonest occupational lung diseases in developed countries with an estimated annual incidence of between 1500 and 3000 cases in the UK.[2] Since the 18th century, medical writers have noted links between certain trades and respiratory symptoms recognisable today as asthma.

OA accounts for 9–15% of asthma in adults of working age.[3,4] Currently, agents that cause OA encompass more than 300 distinct natural and synthetic chemicals. Isocyanates are widely used in many industries and are commonly responsible for most forms of OA. The prevalence of isocyanates-induced asthma in exposed workers is about 10%.[5] However, in most developing countries, including Nigeria, there is lack of adequate data and information about OA. This is particularly disturbing as we are becoming more industrialised. In most other situations the attending physicians have limited knowledge about the diagnostic pathways and management options. This article is, therefore, aimed at providing a simplified approach to OA, especially for general physicians and practitioners in such settings.

Classification and definition

Work-related asthma (WRA) is a broad term that refers to asthma that is exacerbated or induced by exposures in the workplace.[6] It includes OA and work-exacerbated asthma (WEA). The term 'work-exacerbated asthma' refers to asthma triggered by various work-related factors (e.g. aeroallergens, irritants, or exercise) in workers who are known to have pre-existing or concurrent asthma i.e. asthma that is occurring at the same time but is not caused by workplace exposures.[7,8]

The term OA refers to 'de novo' asthma or the recurrence of previously quiescent asthma, i.e. asthma as a child or in the distant past that has been in remission induced by a specific substance at work.[9] It is important to realise that WEA and OA are not mutually exclusive and may coexist in the same worker. In contrast to WEA, the onset of asthma due to work exposures in a person with a history of asthma as a child or in the distant past is considered more likely to be new-onset OA, not WEA, although the recurrent onset of asthma unrelated to work and subsequent WEA is also possible.[9] In summary, WRA encompasses both OA and WEA, which may coexist in individual workers. This discussion will focus mainly on OA.

There are generally two distinct forms of OA. This is based on whether there is a prolonged interval of time between exposure and appearance of symptoms, called latency period (see Table 1):

1.. Immunological OA appears after a latency period of exposure necessary for the worker to acquire immunologically-mediated sensitisation to the causal agent. This type encompasses OA that is induced by an immunoglobulin E (IgE) mechanism (mostly high- and some low-molecular-weight agents) and OA in which an IgE mechanism has not been demonstrated consistently (low molecular-weight agents such as diisocyanates, western red cedar, and acrylates).This form is also called sensitiser-induced OA.
2. Nonimmunological OA is characterised by the absence of a latency period. It occurs after accidental exposure to very high concentrations of a workplace irritant. This clinical entity has also been labelled as irritant-induced asthma.[10,11] The most definitive form of irritant-induced asthma is 'reactive airways dysfunction syndrome' (RADS) occurring after a single exposure to high levels of an irritating vapour, fume, or smoke.[12]

Causative agents

Agents that cause occupational asthma with latency encompass a broad spectrum of natural and synthetic chemicals found in a diverse range of materials and industrial processes.[13]

These agents can be subdivided into those that are IgE-dependent and those that are IgE-independent. Asthma induced by these two groups of agents differs in clinical presentation and the type of reaction produced during inhalation tests. Chlorine and ammonia are the most common of the many agents that can induce occupational asthma without latency. Some examples are presented in Table 2.

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Table 1 Types of occupational asthma

Characteristic	Asthma with latency	Asthma without latency
Clinical		
Interval between onset of exposure and symptoms	Longer	Within hours
Pattern of asthmatic reaction on inhalation testing	Immediate and dual	
Epidemiologic		
Prevalence in exposed population	5–10%	Not known
Host predisposition	Genetics, smoking, atopy, gender	Not known
Pathologic		
Eosinophil change	+++	+++
Lymphocyte change	+++	+
Subepithelial fibrosis	+	+++
Thickened basement membrane	++	+++
Desquamation of epithelium	+	+++

Risk factors for OA

Various risk factors have been identified as risk factors for the development of OA. The most important of these is exposure. In a review of studies on OA with latency, it was observed that there was a direct correlation between the degree of exposure to an occupational agent and the risk of asthma.[14] This concept was supported again by Frew, who stated that, in general, the higher the level of exposure, the more likely the sensitised person is to develop asthma.[15] Once a subject is sensitised, the main factor that influences the onset of symptoms is the degree of exposure.[16] Hence, the level of exposure is a critical factor for the development of OA

However, given the same level of exposure, only a small proportion of workers have been noticed to develop sensitisation and/or OA. This suggests that other factors may be contributory. These include: atopy, rhinoconjunctivitis symptoms, having a measurable PC20, and cigarette smoking. Atopy and smoking are important determinants as regard agents that induce asthma through an IgE dependent mechanism.[13,14] Others include gender and genetics. Gender plays a role in the distribution of occupational lung diseases, since there are gender differences in specific jobs and therefore differences in the exposure to agents causing these diseases.[17] Women report significantly more exposure to cleaning products, biological agents, and textile fibres than men.

Genetic predisposition might be both a confounder and an effect modifier. Implicated are HLA type II and glutathione S-transferase (GST), a family that is critical for protecting cells from oxidative stress products.

Table 2 Common agents that cause occupational asthma

Agent	Workers at risk
High-molecular-weight agents	
Cereals	Bakers, millers
Animal-derived allergens	Animal handlers
Enzymes	Detergent users, pharmaceutical workers, bakers
Gums	Carpet makers, pharmaceutical workers
Latex	Health professionals
Seafoods	Seafood processors
Low-molecular-weight agents	
Isocyanates	Spray painters, insulation installers, manufacturers
Wood dusts	Forest workers, carpenters, cabinet makers
Anhydrides	Users of plastics, epoxy resins
Amines	Shellac and lacquer handlers, solderers
Fluxes	Electronics workers
Dyes	Textile workers
Persulfate	Hairdressers
Formaldehyde, glutaraldehyde	Hospital staff
Agents causing irritant-induced OA (high-level respiratory irritant)	
Spills of chlorine, glutaraldehyde	
Smoke (from fires)	
Accidental high-level chlorine exposure, as in paper mills	

Pathophysiology

Immunological OA: IgE-dependent and IgE-independent

The pathophysiology of immunological OA usually involves an IgE-dependent mechanism. OA induced by IgE-dependent agents is similar to allergic asthma that is unrelated to work.[18-21]

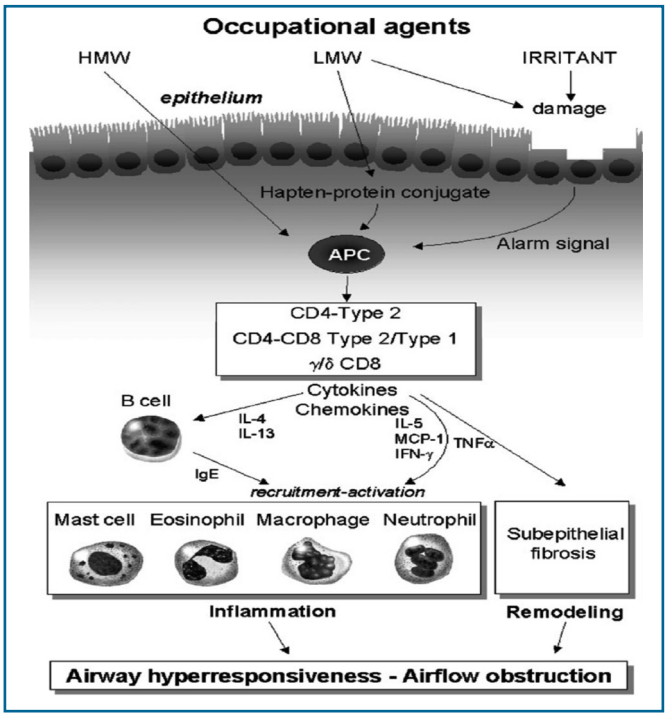

Figure 1 Schematic summary of possible mechanisms in occupational asthma (OA). Causal agents of OA are categorised into high-molecular weight (HMW) and low-molecular-weight (LMW) agents. Exposure to high levels of respiratory irritants can induce irritant-induced asthma. HMW agents are recognised by antigen-presenting cells (APCs) and mount a CD4 type 2 immunologic response leading to production of specific IgE antibodies by interleukin (IL)-4/IL-13-stimulated B cells. Certain LMW agents also induce specific IgE antibodies, probably acting as haptens and combining with a body protein to form functional antigens. However, most LMW agents do not consistently induce specific IgE antibodies. In this type of OA, a mixed CD4/CD8 type 2/type 1 immunologic response or induction of γ/δ-specific CD8 may play a role. Inhalation of high levels of irritants may damage airway epithelium. In subjects who develop irritant-induced asthma, alarm signals from damaged epithelial cells might in turn activate immunocompetent cells. Binding of IgE to their receptors, Th2 (IL-5) and Th1 (IFN-γ) cytokines, and other proinflammatory chemokines (monocyte chemoattractant protein 1 [MCP-1]; tumour necrosis factor [TNF-α]) induce recruitment and activation of inflammatory cells. These cells (mast cells, eosinophils, macrophages, and, in some instances, neutrophils) characterise airway inflammation, which contributes to the functional alterations of OA; that is, airway hyperresponsiveness and airflow obstruction. Subepithelial fibrosis due to thickening of the reticular basement membrane is considered a histopathologic feature of OA. However, the role of this remodelling of the airways in lung function is obscure. (Adapted from Occupational asthma,by Mapp et al. Am J Respir Crit Care Med 2005).[7]

Most high-molecular-weight agents (e.g. flour and animal proteins) induce asthma by producing specific IgE antibodies. Certain low-molecular-weight agents (e.g. platinum salts, trimellitic anhydride, and other acid anhydrides) also induce specific IgE antibodies, probably acting as haptens and combining with a body protein to form functional antigens.[22] Crosslinking of allergens with a specific IgE antibody on the surface of mast cells, basophils, and possibly macrophages, dendritic cells, eosinophils, and platelets, gives rise to a cascade of events that result in the influx and activation of inflammatory cells and in the release of preformed and newly formed inflammatory mediators that orchestrate the inflammatory process (see Figure 1).

Other low-molecular-weight agents, such as diisocyanates and plicatic acid, cause OA that has the clinical and pathologic features of immunological asthma, but do not consistently induce specific IgE antibodies.[23]

Specific inhalation challenge with these low-molecular-weight agents in sensitised individual induces various patterns of asthmatic reactions, including isolated early or late asthmatic reactions, a biphasic reaction, a progressive reaction, or atypical reactions.[24] The airway inflammation process is similar in IgE-dependent and IgE-independent asthma and is characterised by the presence of eosinophils, lymphocytes, mast cells, and thickening of the reticular basement membrane.[25]Increased expression of lymphocyte markers, such as interleukin-2 (IL-2) receptor and CD8+ cells, have been identified as the keys cells in OA with an IgE-independent mechanism for example diisocyanate.[26,27]

Irritant-induced asthma

The mechanism of asthma induced by irritants is unknown.[28] The main target for the initial injury due to inhalation is the bronchial epithelium, which becomes denudated and loses its protective properties. Pathologic changes consist of marked fibrosis of the bronchial wall and denudation of the mucosa.[29]

Natural history and long-term consequences

The risk of OA is highest soon after the first exposure, since most subjects develop asthma within 1 to 2 years of exposure. Nevertheless, the latency period can vary from months to years.[30] The rate of acquiring both sensitisation and asthmatic symptoms may differ according to the nature of the agent and the intensity of exposure.

Diagnosis

Diagnosis of OA should be confirmed by objective testing for asthma and then demonstrating the relation between asthma and work.[31,32] The possibility of OA should be considered in all adults with asthma. A detailed occupational history that covers the past and present, including activities carried out, is an important step in the initial evaluation of the patient. The diagnosis should be confirmed as soon as possible to prevent worsening of symptoms.The assessment should include a detailed history of specific job duties and work processes for both the patient and co-workers. The number and intensity of relevant exposures and the frequency of possible exposure to peak concentrations of potential agents

should be assessed. Safety-data sheets for chemicals in the workplace, industrial-hygiene data, and employee health records may be obtained. A walk-through visit to the workplace may help the physician to understand the work situation better. In general, patients with OA have similar clinical presentations as asthma of non-occupational origin. They present with mild , moderate-to-severe bronchospasm with dyspnoea and wheezing, cough, chest tightness, and even nocturnal symptoms. There may be other extrapulmonary symptoms such as conjunctivitis, rhinitis, and other forms of atopic manifestations. However, they experience some relief when away from work especially in the early stages. Hence, a history of improvement of symptoms when the patient is away from work – for example during weekends and holidays – and a worsening on return to work suggests OA. However, history is not enough for the diagnosis, it should, therefore, be confirmed by objective methods.

1. *Peak flow meter*
Serial peak expiratory flow rate (PEFR) measures are an important investigation when occupational asthma is suspected and have a considerable evidence base.[34-37] With appropriate training and explanation, it is possible to achieve high-quality recordings in workers suspected of asthma. While they are subject to potential falsification and inaccurate transcription, they offer the best and easiest first-line approach to assessing the physiological response to inhaled agents in the workplace. The patient is asked to record PEFR every 2 hours when at work and away from work for about 2–4 weeks. A computer-assisted system [Occupational Asthma System (OASYS)] has been used to provide a simple and validated method for interpretation of serial measurements of PEF (see Figure 2).[34,38]

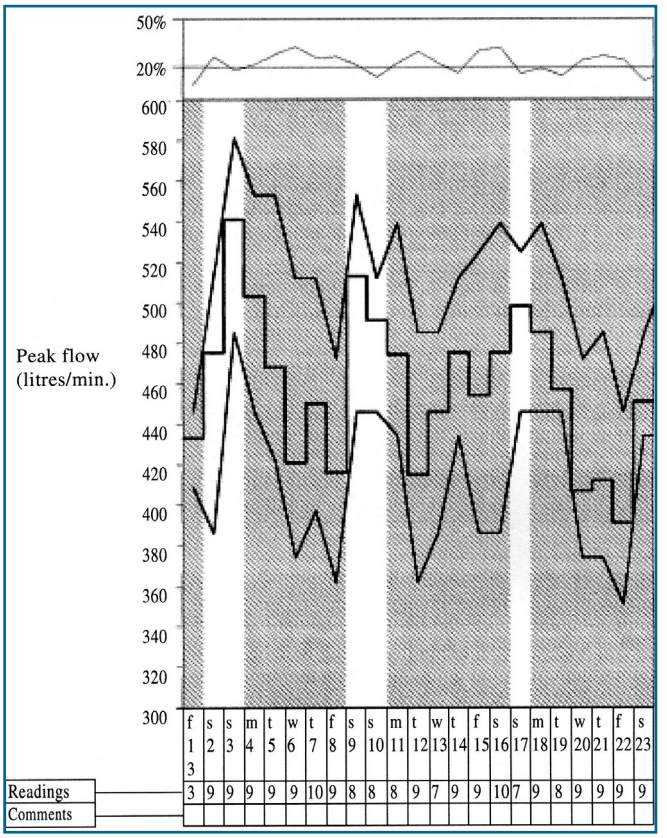

Figure 2 The OASYS plot of a carpenter. The upper panel shows the daily diurnal variation. The middle panel shows the daily maximum (top line), mean (middle line) and minimum (bottom line) PEF. Days at work have a shaded background, days away from work a clear background. There is recovery during each period off work, with variable deterioration on workdays which is likely to reflect variable daily exposures to wood dust. Oasys-2 generates a score of between 1 and 4 for the probability of workdays being worse than rest days. Scores over 2.5 have a 92% specificity for OA and a sensitivity of 70%. The score here is 3.93 confirming occupational asthma. The bottom panel shows the date and the number of readings made each workday. Courtesy Prof P S Burge.[33]

2. *Immunologic tests*
Immunologic tests are useful for demonstrating IgE antibodies to a high-molecular-weight agent, with high values of sensitivity and specificity.[39-44]

3. *Inhalation challenge tests*
There are specific and non-specific challenge tests. Non-specific tests demonstrate airways hyper-responsiveness by measuring PC20 and specific inhalation tests challenge the patient with occupational agents. This seems to be the gold standard. These tests should be carried out only in specialised centres as the test requires the expertise of physicians to monitor the response of a patient in the laboratory and of engineers and occupational hygienists to generate and monitor exposure levels of the causal agent. It is also time-consuming.[45,46] A positive test identifies the cause of OA, provided exposures received are equivalent to those in the workplace. Negative tests do not necessarily exclude OA as the challenge may not adequately reproduce the full extent of the exposures in the workplace. Because only 50% of patients with OA have a positive response on the test and bearing in mind the risk associated with the test ,it may not be considered a routine test for diagnosing OA.

4. *Lung function*
All suspected cases of OA should have forced expiratory volume (FEV) and forced vital capacity (FVC) measured according to agreed criteria. Comparison must be made with a predicted value and the worker's previous lung function, if available.

The use of significant bronchodilator response (15% improvement in FEV1 and at least 200 ml) to help make a diagnosis of asthma should be consistent with any of the existing asthma guidance.[47] Such measures may help to distinguish between asthma and chronic obstructive pulmonary disease (COPD), although clearly workers with smoking-related COPD may also develop OA. The role of other guidance is important here, with particular relevance to oral or inhaled steroid trials. Pre- and post-shift measures

of FEV1 are not generally helpful to either confirm or refute a diagnosis of OA.[47]

5. *Analysis of induced-sputum*
This is a valid and reproducible method for studying airway inflammation.[48] The finding of neutrophil inflammation, documented by an increase of neutrophils in induced sputum, after exposure to low-molecular-weight agents, is less common.[49,50]

Several studies have documented increased eosinophil count in OA caused by both high- and low-molecular-weight agents.[51,52]

Management

1. Avoidance
The ideal treatment for patients with OA with a latency period is removal from exposure. A worker might be transferred to a job without exposure to the offending agent in the same company. When asthma is induced by a workplace sensitiser, strict exposure control is needed. For employees sensitised to low-molecular-weight agents (e.g., isocyanates), complete cessation of exposure is the most desirable intervention. For patients with OA induced by an acute exposure to an irritant at work, steps should be taken to prevent further exposure to high concentrations of the irritant.[47]Apart from avoidance, other measures like substituting the work process with a non-toxic material and enclosure of industrial process are equally important steps.

2. Standard asthma therapy
The treatment of OA does not differ significantly from the management of asthma that is not work related.[47,53] Patients diagnosed with OA should have medical treatment following published asthma guidelines. Patients should be placed on treatment commensurate with the severity of their asthma symptoms. Because of the airway inflammation in OA, steroid still occupies a main place in treatment. The beneficial effects of steroids are more evident when treatment starts soon after diagnosis. Patients with pre-existing asthma that is aggravated at work should optimise anti-asthmatic pharmacologic treatment. Like other chronic diseases, OA can cause loss of productivity, which can be reduced by pharmacologic treatment.

3.Long-term management and monitoring of OA disease
The majority of patients with OA with latency do not recover, even several years after cessation of exposure. They have permanent impairment or disability.[14] Important determinants of recovery are the total duration of exposure, the duration of symptoms, the severity of asthma, the lung function, the degree of airway hyperresponsiveness at the time of diagnosis, and the duration of follow-up.

Because of the socio-economic impact and implications of OA, proper assessment of impairment and proper management of patients with OA and with work-aggravated asthma are important.[54] The assessment for temporary disability should be performed immediately after the diagnosis of OA is made, and long-term assessment of impairment should be performed for 2 years after cessation of exposure, since the maximum rate of improvement occurs in the first 2 years after cessation of exposure.

Clinicians should also support the patient in the pursuit of appropriate compensation. In many countries, compensation systems for OA are unsatisfactory because they largely underestimate the social and occupational damages.

Prevention and surveillance
Primary prevention
Host and environmental factors should be taken into consideration. Primary prevention of OA can be achieved by carrying out a comprehensive risk assessment of the workplace, allowing reduction in exposure to asthmagens and through an appropriate health surveillance programme. These will allow the identification of hazards with unacceptable risk while the latter will allow a responsible person in the workplace to identify workers at risk of allergic (or irritant) disease during pre-employment, pre-placement screening, and ongoing health surveillance. Exposures in the workplace should be low enough to prevent the onset of asthma in all workers, irrespective of their individual susceptibility.[55]

Secondary prevention
Preclinical changes in the disease should be identified. Secondary prevention of OA will also potentially arise as part of a health surveillance programme. Once markers of early possible OA are identified, removal from exposure may lead to regression of these symptoms, preventing progression to established and disabling disease.

Tertiary prevention
Workers should be diagnosed in an early phase of the disease and appropriate management of the disease should be offered. Tertiary prevention is largely concerned with reducing the disability associated with OA in workers already diagnosed with this condition. The standard advice given to such workers is that further exposure to allergens known to cause their asthma is unadvisable.

Conclusion

OA is a disease with enormous medical, social, and legal consequences. As society gets more industrialised, it is likely that more cases of OA will be diagnosed. In most developing countries, including Nigeria, cases are still under diagnosed. Exposure control, regular audit of processes, and education of the workers and employers are important factors in controlling the disease.

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