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Focus on work-related asthma

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Summary
Work-related asthma, encompassing both occupational asthma and work-exacerbated asthma, accounts for 10%-25% of adult asthma in Europe and occupational asthma is currently one of the most common forms of occupational lung disease in many industrialized countries. It is cause of direct and indirect costs for the worker, the employer and the society and it is probably still underdiagnosed. Hence, the possibility of work-related asthma should be considered in all adult patients in whom asthma started or worsened during their working life. The investigation of WRA includes assessing the presence of asthma, and demonstrating its work-relatedness, that requires training and expertise. Due to the frequent association of occupational asthma and rhinitis, the presence of both upper and lower airway symptoms should be investigated. Furthermore, since is work-related asthma is a preventable disease all efforts should be made for effective prevention strategies.

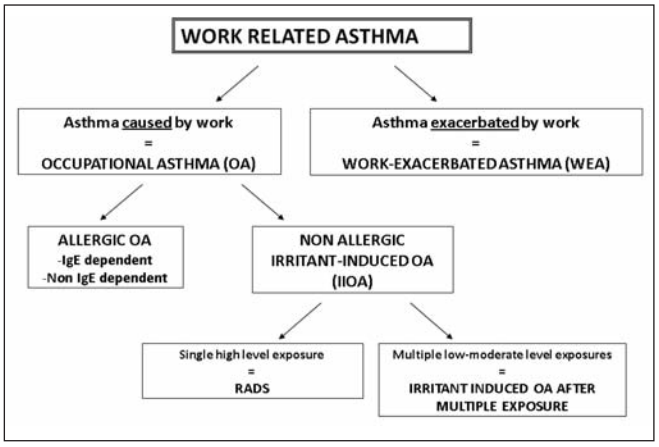
Introduction

There is accumulating evidence that workplace exposures contribute substantially to the global burden of asthma. In Europe the fraction of adult asthma attributable to occupational exposure ranges between 10% and 25% (1).
Work-related asthma (WRA) refers to at least two nosological entities. The first is *occupational asthma* (OA), namely asthma "caused" by workplace exposure, which may recognize an allergic or irritant causal mechanism. The second entity is personal asthma that worsens at work, named *work-exacerbated asthma* (WEA) (2-4) (Figure 1).
Occupational asthma is currently one of the most common forms of occupational lung disease in many industrialized countries (5) but it is probably still underdiagnosed (6). OA is often associated with serious personal and socioeconomic consequences, therefore an early recognition and a correct diagnosis are important to reduce or limit the consequences of the disease (4).
The purpose of this review is to summarize the scientific evidence on WRA, to discuss the diagnostic strategies and the management, and to illustrate the medicolegal aspects pertaining this relevant occupational disease.

Classification of WRA

Occupational asthma
Two types of OA are distinguished (2):
1. *Allergic OA:* OA induced by sensitizers, which appears after a latency period between the beginning of exposure and the onset of symptoms. This type of OA may be

Figure 1 - Classification of Work-related asthma (adapted from ref 2)



caused by high- (HMW) and some low-molecular-weight (LMW) agents (Table 1) for which an IgE-mediated mechanism has been proven, and by some specific LMW agents in which the allergic mechanisms responsible have not yet been fully characterized.

2. *Non allergic, irritant-induced OA (IIA).* The most definite form of IIOA is the "Reactive Airways Dysfunction Syndrome" (RADS), which occurs as an acute onset of asthma after a single exposure to high concentrations of an irritating gas, vapour, fume or smoke (7). The term IIA has been often used to denote various forms of asthma related to irritant exposures at work in which the onset of asthma is not so sudden and follows multiple less massive exposures to irritants (8). These types of IIA are currently under re-definition and classification by an *ad hoc* EAACI Task Force.

Allergic OA is the most common type of OA, accounting for more than 90% of cases (9).

Work exacerbated asthma

The term Work Exacerbated asthma (WEA) 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, (*e.g.*, asthma that is occurring at the same time but is not caused by workplace exposure) (2). WEA has been reviewed recently (3).

Table 1 - Causal agents of occupational asthma and occupations at risk.

Agent	Occupation
High molecular weight agents	
Flour(s), α-amylase, other enzymes, egg white	Baking, milling, pastry making
Rat, mouse, guinea pig, ferret, etc. proteins, egg	Laboratory animal researchers and technicians
Latex	Health care workers
Detergent protease, amylase, lipase, cellulase	Detergent enzyme manufactures
Herbal teas, green coffee bean	Tea packers, coffee processors
Prawn, crab, other (shell) fish proteins	Sea food processors
Garlic, egg, enzymes	Other food processors
Pollens	Flower and vegetable farmers
Low molecular weight agents	
Diisocyanates	Spray painters, French polishers
Colophony fume	Electronic solderers
Glutaraldehyde, methyl/butyl methacrylate	Health care workers
Diisocyanates, acid anhydrides, epoxy resins	Plastic and foam manufacturers
Red cedar, iroko, other tropical sawdusts	Woodworkers, lumberjack
Reactive dyes	Textile workers
Persulphates	Hairdressers
Penicillins, morphine, cimetidine	Pharmaceutical manufacturers

Causal agents and mechanisms

Allergic OA may be caused by HMW proteins derived from animals or vegetables which act as complete antigens through an IgE-mediated mechanism similar to that of non occupational allergic asthma. The same mechanism is strongly suggested, although not definitely demonstrated, for some LMW organic and inorganic compounds (*i.e.*, platinum salts, trimellitic anhydrides, other acid anhydrides) which probably act as haptens, binding with body proteins to form functional antigens (4).
More than 300 substances have been identified as causal agents of OA. Lists are available in textbooks [16], and websites (www.asmanet.com, www.asthme.csst.qc.ca, www.eaaci.net). New causal agents are reported each year, and OA can be caused by agents not found on existing lists. In many sectors, such as health care, hairdressing, cleaning, farming, baking, auto body repair, fire fighters or other emergency responders, workers are exposed to multiple agents.

Non allergic, irritant-induced OA
Numerous different exposures have been associated with these types of OA. The causal association has been most strong in reports of RADS, the acute form type of irritant-induced OA . The original description by Brooks (7) was from accidental exposures to uranium hexafluoride, floor sealant, spray paint, 35% hydrazine, heated acid, fumigating fog, metal coat remover, fire, and/or smoke (in 10 subjects).
In the report which firstly used the term "irritant-induced OA" and modified Brooks' criteria to multiple high level exposures (8) the causative exposures were to calcium oxide dust, acid fumes, chlorine, paint fumes and accidental high level exposures to diisocyanates.
Inhaled irritants provoke an acute inflammatory response causing injury to the epithelial and other residential cells of the lungs, however the ultimate pathogenic mechanisms of IIA remain mostly unknown in most cases. Based on available literature, the pathogenic mechanism apparent during the acute phase resembles a toxic mechanism, although the long-term phase seems similar to allergic OA.

Association with rhinitis

Occupational asthma is very often associated to rhinitis (up to 92% of cases in the case of OA caused by HMW-agents) (10). Symptoms of rhinoconjunctivitis often precede the onset of asthma, particularly in the case of HMW-causal agents, and rhinitis may be considered an early marker of OA (11-12) .
Occupational asthma and occupational rhinitis share the same causal agents, and immunologic mechanisms(12) The most important link between rhinitis and asthma is the presence of inflammation of the nasal and bronchial mucosae(13). The model of United Airways Disease has been confirmed also for some occupational sensitizers (14).
In a recent study a high frequency of work-related rhinitis symptoms (83%) has also been reported in subjects with work related asthma (15).

Diagnosis of WRA

The possibility of WRA should be considered in all adult patients who are currently employed, and in those in whom asthma started or worsened during their working life. A suggestive history is the cornerstone for raising the suspicion and starting the diagnostic workup. Both an accurate clinical and occupational history should be collected (2). Due to the frequent association of occupational asthma and rhinitis, the presence of both upper and lower airway symptoms should be investigated. Assessment and documentation of exposure is necessary. History may be highly suggestive, but it is not sufficient for a definitive diagnosis and objective tests should be performed (2,4,18).

Diagnostic work-up
The investigation of WRA includes assessing the presence of asthma, and demonstrating its work-relatedness (2,4,18).

Assessment of the presence of asthma.
Asthma should be confirmed by means of spirometry, bronchodilation test, assessment of non-specific-bronchial-hyperresponsiveness (2,4,18). The assessment of bronchial inflammation by means of sputum analysis and/or measurement of exhaled nitric oxide levels is an important supplemental investigation and is a key step for diagnosing eosinophilic bronchitis an entity recently described (13) . The diagnosis of a concomitant rhinitis should be confirmed by objective methods including nasal examination, physiological assessment (nasal patency, nasal inflammation, non-specific-nasal hyperreactivity) (12).

Immunological investigations

When the involvement of a HMW agent or a LMW agent inducing an IgE-mechanism is suspected (*allergic OA*) skin prick tests and determination of specific IgE antibodies should be performed to demonstrate the sensitization to occupational allergens. Nevertheless, since sensitization alone does not mean allergy, the demonstration of the link between the specific sensitization and work-related changes in lung function is mandatory for the diagnosis of WRA. Standardized tests are available only for a few allergens, consequently, in many cases patients are tested with non commercially available, laboratory made skin test extracts and IgE tests. Before accepting the results from such tests proper control tests in non-exposed subjects and in case of new allergens additional challenge tests are required (2).

Assessment of work-relatedness of asthma

Since 1979 serial measurements of peak expiratory flow rate (PEFR) have been used as an objective confirmation of the relationship between the workplace and asthmatic symptoms. One important advantage of PEFR monitoring is the measurement of lung function during a realistic exposure (16), however this method has several limitations, e.g. need of good cooperation, possible falsification, feasibility of measurement away from work, no identification of the causative agent and in most cases it is not enough for reaching a definite diagnosis.

The specific inhalation challenge (SIC) in the laboratory is considered a reference standard for the diagnosis of OA induced by sensitizing agents (4, 17). SIC exposes workers with suspected OA to suspected causal agents in a controlled setting, to demonstrate a direct relationship between exposure to that agent and asthma (17). SICs have some limitation including possibilities of false negative results and lack of usefulness in the diagnosis of non allergic OA. In addition, SICs may be performed in only a few centres provided by specialized facilities and expertise, and when a suspected workplace agent has been identified. SICs are indicated when other objective methods are not feasible, have failed, or provide equivocal results, and when a new (not formerly described) specific cause of OA is suspected. (4,17).

Diagnosis of Non allergic, Irritant-Induced Occupational Asthma

Diagnostic criteria for RADS, the acute form of irritant-induced OA, initially proposed by Brooks (7) and adopted by ACCP (4), are summarized in Table 2.

The same criteria might be adopted for diagnosis of non acute forms of irritant-induced OA, except for the onset of asthma, that in these form occurs after multiple, low-to-moderate level exposures to irritants (8). The definite diagnosis of these forms is often difficult on a clinical basis since often it should be differentiated from WEA, or from coincidental asthma that is not work-related

Diagnosis of WEA

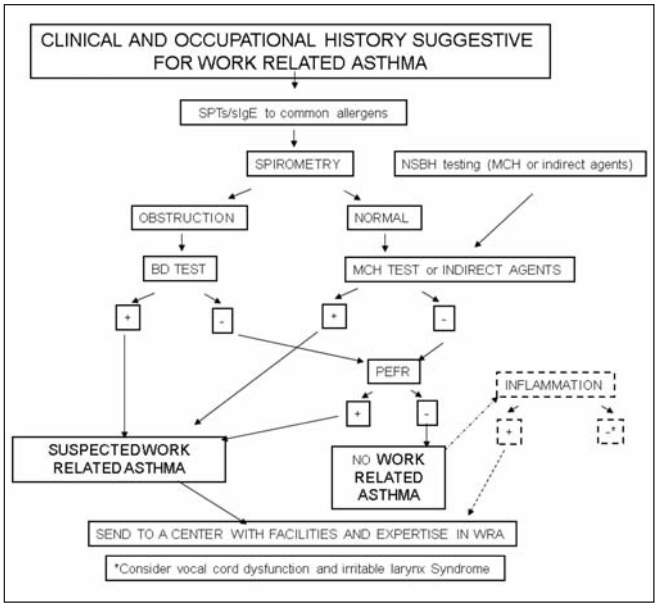
WEA has been diagnosed most commonly by self-report of worsened asthma symptoms on the job in workers with pre-existing asthma. Nevertheless, a definite WEA diagnosis should be based on "objective indicators" of worsening of asthma and of deterioration of pulmonary function related to work environment. Since OA and WEA may coexist SICs can be useful to exclude sensitization to a specific agent and consequently OA (2).

The evaluation of WRA requires training and expertise. Timely and accurate diagnosis of OA is a key element for advising appropriate treatment interventions and minimizing the adverse health and socioeconomic outcomes (2,4, 18). The role of allergologists and/or of other specialists dealing with asthma is of primary importance in raising the suspicion of WRA from the clinical history, in performing a series of investigations in their daily practice (Figure 2) and if the suspicion is confirmed, in referring the patient to a specialized centre in order to confirm the work-relatedness of asthma, and make the definite diagnosis. A recent EAACI Position paper has provided an *ad hoc* algorithm based on two different levels of diagnosis (2).

Table 2 - Diagnostic criteria for the Reactive Airways Dysfunction Syndrome (RADS) [adapted from Brooks (ref 7) and the American College of Chest Physicians guidelines (ref 4)]

Absence of preexisting asthma or a history of asthma in remission
Onset of asthma symptoms after a single inhalational exposure or accident
Exposure to an irritant vapor, gas, fume, or smoke in very high concentration
Onset of asthma symptoms within minutes to hours and less than 24 h after the exposure
Presence of non-specific bronchial hyperresponsiveness with or without airflow obstruction
Exclusion of other pulmonary disorders that can explain the symptoms or simulate asthma

Figure 2 - Basic investigations for WRA (adapted From ref 2)



Management Of Wra

The management of WRA includes environmental measures, appropriate therapy, assessment of impairment, a medicolegal approach and rehabilitation programmes, whenever possible. (4, 18-19).
For *allergic OA* removal from exposure is recommended in guidelines as the most effective treatment to improve symptoms and asthma outcome (4,18), however, there is evidence that less than one-third of affected workers who cease exposure recover (20). Moreover, removal from exposure is often not feasible, or is associated with substantial adverse economic consequences for the worker, and the society, thus reduction of exposure as an alternative to removal and the optimal management option for OA have recently been evaluated in systematic reviews of the available literature (20-21). The results of these reviews have shown that reduction of exposure seems to be less beneficial than complete avoidance, and that persistent exposure to the causal agent is more likely to result in asthma worsening than complete avoidance. Therefore, from a clinical point of view reduction of exposure cannot be routinely recommended as an alternative to cessation of exposure in the management of allergic OA. However, another Cochrane review evaluating the effectiveness of workplace interventions on the outcome of OA concluded that since removal from exposure is associated with an increased risk of unemployment, whereas reduction of exposure is not, the clinical benefit of removal from exposure or exposure reduction should be balanced against the increased risk of unemployment (22).

Pharmacologic treatment of allergic occupational asthma is carried out according to current asthma Guidelines (23). Information on the effectiveness of specific immunotherapy with high molecular weight occupational allergens are still scarce, and not evidence based (20).

The data on management of *irritant-induced OA* are scarce, however these subjects who are not sensitized to work agents can often continue to work in the same environment with appropriate asthma therapy and close environmental control unless their asthma is severe.

Patients with *work-exacerbated asthma* might be able to continue working with a close environmental control and optimization of asthma treatment, while more severe cases may require a change in jobs (3).

Medicolegal aspects

Every physician who makes a diagnosis of occupational asthma should report to authorities and to the National Insurance Institute. OA is a compensable disease in many countries, strictly depending on the rules of each country compensation system, with greatly differs from country to country. Compensation is granted if objective disability exists (but not if only impairment exists) (19).

Socio-economics and costs

Work related asthma is cause of direct and indirects costs for the worker, the employer and the society (19).
In UK The estimated total lifetime cost of new cases of occupational asthma in the year 2003 were between £25.3 and 27.3 million (24).
The direct costs (i.e. medications, physician consultations, emergency room visits and hospitalisations) are similar on average for occupational and non-occupational asthma of similar severity (19). Indirect costs affect the worker, the employer and the state. The worker suffers loss of income. The costs for the employer include lost productivity from sickness absence and labour turnover, and compensation and insurance costs. The costs for the state include compensation, unemployment support and loss of tax rev-

enues. The economic cost mainly falls on the worker and the state, not on the employer (24).

Prevention

WRA is a preventable disease and all efforts should be made for effective prevention strategies.
Environmental control is the cornerstone for prevention, and workplaces should be kept as healthy places (25). Exposure elimination is the strongest and preferred primary preventive approach to reduce the burden of OA. If elimination is not possible, exposure reduction is the second best option for primary prevention of OA. However it should be emphasized that occupational exposure standards exist for a minority of the approximately 300 occupational respiratory sensitizers, and that there is no exposure level which entirely eliminates the risk, so the focus should be on benchmarking and minimization of exposure (26). Structure–activity analysis is a easy method which can predict the likelihood of LMW chemicals being respiratory sensitizers. Nevertheless, it is so far only validated for chemicals <1000 daltons (27). The evidence for the effectiveness of personal devices in preventing OA is limited (26).
In IIA as well environmental measures include elimination of irritant products where possible, and where this is not possible, control of exposures to safe levels.

Identification of pre-employment individual risk factors such as atopy, preexisting asthma, particularly if severe, and/or non specific bronchial hyperresponsiveness, which may increase the risk of developing sensitization and WRA, is also important. However the presence of such factors, including atopy, should not be intended to exclude the individual from work but to give appropriate advice and reinforce environmental control (18).
Workers' information and education to adopt all measures to limit occupational exposure to potential allergens and respiratory irritants is regarded as important for prevention. Since apprenticeship is recognized as a period of increased risk of developing work-related respiratory allergic diseases, young people are considered a special category to be reached by adequate information on work-related risks through education campaigns, which should be addressed also to schools, teachers, health care personnel and employers. (25). Primary physicians, pediatricians and allergologists can play a pivotal role for this scope.
Medical surveillance of exposed workers and apprentices is the secondary prevention measure for WRA. It is generally accepted that sensitization to occupational agents precedes the development of rhinitis and asthma symptoms, and rhinitis symptoms precede the onset of asthma, therefore prevention of sensitization and/or early identification of rhinitis represents a crucial point in prevention of allergic OA (12). Exposed workers and apprentices should be educated to recognize and to report immediately all possible symptoms suggestive of onset of work-related rhinitis and/or asthmatic symptoms, or of work-related exacerbations, to health care personnel, since, as stated above, early diagnosis of OA followed by prompt appropriate treatment and environmental interventions increases the likelihood of recovery (2,4).
Identification of an index case of OA and its etiology may be important for implementing primary preventive measures for other exposed workers.
In workers exposed to irritants especially in jobs in which with a high frequency of asthma symptoms has been reported, such cleaners (1), medical surveillance might play a role to detect cases of non acute, chronic irritant-related asthma.
Tertiary prevention of WRA involves medical management of asthma to minimize impairment, workers' compensation and rehabilitation programmes (4).

Conclusions

In conclusion WRA is common, and OA is the most frequent type which can lead to permanent disability, decreased quality of life, sickness absence and increased costs for the patient and society. However, the disease still seems to be underestimated. The prognosis of OA is frequently worse than non WRA cases, but may improve with early diagnosis and removal from exposure. Effective preventive interventions to reduce the burden of OA have both a health and a strong economic justification. Nevertheless, since the economic cost mainly falls on the worker and the state, not on the employer, the incentive for employers to act is week. The role of physicians and of Scientific Societies in increasing the knowledge of this disease, and in improving diagnosis and timing interventions is crucial and might be a challenge for the future.

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