

# OCCUPATIONAL ALLERGIES: A BRIEF REVIEW

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## ABSTRACT

Occupational allergies are groups of work-related disorders that are accompanied by immunologic reaction to workplace allergens and include occupational asthma, rhinitis, hypersensitivity pneumonitis, dermatitis, and anaphylaxis. This mini review presents a brief analysis of the more important aspects of occupational allergic disorders.

**Keywords:** Occupational allergies, asthma, rhinitis, dermatitis, hypersensitivity pneumonitis, anaphylaxis.

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## INTRODUCTION

The epidemiologic features of diseases have changed since the industrialisation and civilisation of modern society, particularly in the second half of the 20<sup>th</sup> century. The significant increase in prevalence and diversity of occupational allergies (i.e. occupational asthma [OA], rhinitis, dermatitis, hypersensitivity pneumonitis, and anaphylaxis) is part of this alteration, in both developed and developing countries.<sup>1</sup> Occupational allergy should be considered a real challenge, therefore early detection is highly recommended. Missed or untreated occupational allergy, either by workers or employers, may lead to continuous exposure, progressive health problems, and worsening of the medical condition. Consequently, mild-to-severe medical injuries or pathologic conditions, together with job loss and economic burden, could occur.<sup>2</sup>

Usually, the entire body of a worker with a certain genetic background is affected by allergens in the workplace. Skin and respiratory systems, the first exposed organs, are the most frequent roots of occupational exposure, which may cause local or systemic allergic (immunologic) disorders. On the other hand, it is demonstrated that skin exposure may result in respiratory reaction and vice versa.<sup>3</sup> Therefore, occupational allergies in both skin and respiratory systems should be considered jointly.

## OCCUPATIONAL ASTHMA

### Definition

According to the American College of Chest Physicians (ACCP) consensus statement, every occupation-related asthma is classified under the broad term of work-related asthma (WRA), which includes: OA (*de novo* asthma induced by exposure in the workplace) and work-exacerbated asthma (WEA; aggravation of pre-existing or concurrent asthma due to work-related factors, such as aeroallergens, irritants, or exercise). OA includes sensitiser-induced asthma (asthma associated with immunologic and allergic mechanism) and irritant-induced asthma (which occurs due to aspiration of a great amount of an irritant material in the workplace) (Table 1).<sup>2,4-6</sup>

Although the distinction between OA and WEA may be very difficult, it is of paramount importance due to the differences in treatment, prognosis, and legal aspects.<sup>7</sup> The coexistence of OA and WEA in a patient could be confusing. In patients with history of well-controlled childhood or long-past asthma, the onset of asthma following workplace exposures is classified as new onset OA rather than WEA. Meanwhile the recurrence of asthma after non-occupational exposures is considered as WEA.<sup>4</sup>

**Table 1: The classification of work-related asthma.**<sup>2,4,6</sup>

<b>Work-related asthma</b>
<b>Occupational asthma</b> <ul style="list-style-type: none"><li>- Sensitiser-induced asthma (allergic)</li><li>- Irritant-induced asthma (non-allergic)</li></ul>
<b>Work-exacerbated asthma</b>

## History

Since the 18<sup>th</sup> century, physicians have explored the association of certain trades with progression of respiratory symptoms. The list of asthma causative or triggering factors in workplaces was developed further during the 20<sup>th</sup> century, especially by the mid-1980s, resulting in hundreds of distinct causes of OA being recognised thus far.<sup>4</sup>

## Epidemiology

WRA is the most common type of occupational pulmonary involvement.<sup>8</sup> Although its prevalence has not been reported definitely, it is estimated that up to 25% of adult asthma patients have WRA.<sup>4,9</sup> On the other hand, it is believed that attributable risk of OA in adult asthma is nearly 15%. Higher prevalence is seen in individuals exposed to chemicals (e.g. painters, welders, etc.), animal handlers, woodworkers, cleaners, healthcare workers (9% of cases), those working in food processing, and so on.<sup>2,10-12</sup> Conversely, some studies showed no increase, or even decrease, in the prevalence of respiratory allergies in farming and textile industries, consistent with the so-called 'hygiene hypothesis'.<sup>13,14</sup> Well-recognised high WRA risk groups are females, smokers, those with history of upper airway symptoms and bronchial hyper-responsiveness, and those with certain hereditary factors, atopic histories, and frequent exposure to high amounts of causative factors.<sup>2,5</sup>

## Pathophysiology and Causative Agents

The disease is induced by the interaction of multiple intrinsic (i.e. genetics) and extrinsic (i.e. environmental) factors, similar to other non-communicable chronic diseases. Therefore, new discoveries in the fields of molecular pathology and genetics, along with prevention of exposure to environmental causative agents, has markedly decreased the prevalence of WRA.<sup>2,9</sup> The increasing list of known causative factors of WRA (>400) contains both high molecular weight (HMW) antigens (i.e. biologically derived substances

>10 kDa such as the proteins and glycopeptides produced by animals, plants microbes, etc.) and low molecular weight (LMW) antigens (such as chemicals and metals). Although HMW antigens were the most common cause of conventional OA, the role of LMW antigens has been emphasised recently.<sup>2,4,9,15</sup> WRA occurs through the immunoglobulin E (IgE)-mediated reaction to HMW antigens. Meanwhile, the LMW antigens work either as haptens to provoke immunologic reaction, or via an unknown mechanism.<sup>9</sup>

## Diagnosis

WRA is diagnosed based on a confirmed asthma diagnosis plus evidence of workplace exposure worsening symptoms. Early diagnosis is an advantage for patients. Generally, there are limited standardised tests for workplace antigens. Thus, OA diagnosis is not based on straight forward laboratory tests.<sup>9</sup> Taking complete medical histories, performing physical examinations, appropriate imaging, and laboratory tests, together with clinical impressions of WRA, are the key points for diagnoses.<sup>16</sup> Questionnaires are only acceptable when used as screening tools because of their lack of specificity. The standard pulmonary tests detecting increased airway hyper-reactivity associated with occupations would be useful diagnostic tools. Meanwhile, the high sensitivity and specificity of daily, continuous peak flow evaluation has proven the most useful method. The specific antigen inhalation challenge test is the gold standard for diagnosis of sensitiser-induced asthma and detection of new antigens. In general, it is not a requisite test because of potential risks, possible false positive and negative results, and requirement of highly specialised equipment; particularly when other methods can be used. Immunologic tests can be used to identify HMW antigens in sensitiser-induced asthma;<sup>2,5,17</sup> specific IgE and skin-prick testing are highly recommended in this regard.<sup>18</sup> Meanwhile, detection of specific IgE against HMW antigens is not commonly available.<sup>2</sup> Evidence shows that component-resolved diagnostics may be used to clarify the allergens (e.g. in baker's asthma),<sup>19</sup> thus development of a protocol for component-resolved diagnostics usage was attempted.<sup>20</sup> Unfortunately, despite these efforts, no ideal biomarker has been found yet.<sup>17</sup> To avoid unnecessary asthma treatment, OA diagnosis should be differentiated from work-associated irritable larynx syndrome, which is actually laryngeal irritation induced by exposure to LMW irritants in workplaces.<sup>21,22</sup>

## Management

Patient quality of life can be severely affected by WRA, and depression and anxiety incidence in individual WRA is about 50%, which is more common than in asthma. Thus, treatment should be considered seriously.<sup>9</sup> The mainstay of every policy in WRA management is early reduction or eradication of exposure factors if possible.<sup>2</sup> This is the main reason to distinguish WRA from non-OA.<sup>23</sup> Furthermore, medical treatment of WRA should be conducted according to asthma guidelines. It should be noted that drug treatment should be accompanied with exposure avoidance. However, in WEA or irritant-induced asthma, patients could return to the same role in an exposure-free environment following asthma control.<sup>2,23</sup> The antigen-specific immunotherapy may be effective in sensitiser-induced asthma with known causative agents.<sup>24</sup> Prognosis is determined by early diagnosis, removal of exposures, patient age, respiratory function at the time of diagnosis, and exposure duration. However, several years of exposure avoidance and medical management are usually required before judgement may be made on a complete cure.<sup>2,6</sup>

## Prevention

As the primary prevention, the first step is to remove all causative factors from a workplace.<sup>25</sup> If this is not applicable, use of less irritating alternatives in addition to provision of good personal protection and appropriate ventilation may be beneficial. Pre-employment medical work-ups are not always diagnostic. As secondary and tertiary prevention, periodical workplace inspection, and medical check-ups and treatment by occupational and pulmonary physicians will be useful.<sup>2,25</sup>

# OCCUPATIONAL ALLERGIC RHINITIS

## Definition

Occupational allergic rhinitis (OAR) is characterised by induction or worsening of IgE-mediated sneezing, watery rhinorrhoea, and nasal congestion, due to inhaled exposure to work-derived agents.<sup>2</sup> These symptoms may be intermittent or persistent following a latency period after exposure.<sup>26,27</sup> In contrast, non-allergic rhinitis has no immunologic bases or latency period and may be seen just after a single high-dose exposure.<sup>28</sup>

## Epidemiology

The prevalence range of OAR has been reported at 0.2-18% in the general population<sup>2,26</sup> and at 2-87% of exposed workers.<sup>27</sup> It is believed that OAR is underestimated and underdiagnosed, but is still more frequent than OA.<sup>26</sup> Up to 90% of asthmatics suffer from rhinitis while only one-third of rhinitis cases have concomitant asthma.<sup>29</sup> Changes to work environment and subsequently to allergic factors may change the epidemiology of OAR.<sup>2</sup>

## Causative Agents

Similar to other allergic conditions, hundreds of causative factors have so far been recognised for OAR.<sup>15,28</sup> HMW mould, animal or plant derivatives, and LMW chemical substances (such as haptens) in workplaces may induce OAR.<sup>2,29,30</sup> OAR is more prevalent in bakers, kitchen workers, waste collectors, cleaners, healthcare staff, hairdressers, and agricultural and textile industry workers.<sup>26,29,31,32</sup>

## Mechanisms

Genetic backgrounds are considered to be substantial factors in the occurrence of asthma and allergy,<sup>33-35</sup> and it is reasonable to postulate that genetic predisposition may lead to OAR, due to IgE-mediated immunologic reaction to allergens.<sup>2,27</sup> This reaction includes Type I (IgE-mediated) hypersensitivity reaction, while Types III and IV may also occur. The classification and severity of OAR is important for selecting treatment options.<sup>2</sup>

## Diagnosis

Identification of allergic factors is not easy, but could be achieved with an exact medical history, immunologic examination, and nasal mucosa tests. Although detection of nasal-specific IgEs against chemical allergens is useful for specific diagnosis, it is not feasible in many centres. Meanwhile, the nasal provocation test for allergens is highly valuable for diagnosis confirmation.<sup>2,26</sup>

## Management

OAR interferes with personal life and induces personal restrictions, decreased productivity, and work disruption. Furthermore, continuous exposure to workplace allergens could progress OAR to WRA and more severe forms of airway involvements. Therefore, allergen exposure avoidance together with the appropriate drug therapy is the best treatment approach. Immunotherapy and

surgical therapy (in some cases) could also be effective.<sup>2,36</sup>

## Prevention

Similar to occupational asthma, three levels of prevention may be used for OAR.<sup>25</sup> The highest priority is early detection and elimination of allergens in the workplace. It may be performed using policies such as substitution with alternative non-allergen substances, or complete elimination of allergens and appropriate ventilation, although the latter is less effective. Respiratory protective tools, such as masks, may reduce the allergen dose, but protection quality depends on specification and qualification of the mask and the size and type of allergens. The pre-employment evaluation of workplaces may not be always effective in allergen prevention, but continuous education of employers and employees is more useful.<sup>2</sup>

## OCCUPATIONAL HYPERSENSITIVE PNEUMONITIS

### Identification and Classification

As a complex syndrome, occupational hypersensitive pneumonitis (OHP) occurs following repetitive exposure and inhalation of a wide variety of sufficiently small (<5 µm) organic particles in the workplace. These particles can reach alveoli and provoke an exaggerated immune response of small airways, parenchyma, and pulmonary alveoli. The causative particles may be derived from excretory substances and animal body constituents, floating fungi and bacteria, protozoa, insect proteins, and LMW organic or inorganic chemical compounds.<sup>2,37</sup> Based on symptoms and type of onset, OHP can be classified as acute, subacute, or chronic.<sup>2,38</sup> However, as classifications overlap, cluster analysis has suggested a division of these classifications into two clusters.<sup>16,39</sup>

### Epidemiology

Generally, the prevalence of OHP varies in different conditions,<sup>38</sup> however pneumonitis is more prevalent in the regions and time periods with higher probability of exposure to causative factors. Following higher detection of OHP, diagnosis rates are increasing. As previously mentioned, accurate estimation of epidemiologic features of OHP is difficult because OHP is influenced by the type of causative factors and the nature of exposure.<sup>2</sup> The severity, duration, and frequency of exposure are considered as extrinsic risk factors of OHP.

Thus far, no demographic or genetic risk factors have been discovered.<sup>2,40</sup> The mortality rate of OHP is low, particularly in females and non-elderly people, but increases in chronic forms which are mostly accompanied by pulmonary fibrosis.<sup>2,41</sup>

### Causative Agents

Aetiology, natural history, and pathogenesis of OHP are not well described in current publications.<sup>40</sup> However, it has been recognised that important causative antigens (i.e. proteins and chemicals) are: plant powder and dust, animal body constituents and excretory substances, insects, fungi, bacteria, drugs, organic chemicals, and so on. It is also believed that LMW chemicals (such as zinc, inks, dyes, and isocyanates, etc.) and especially metal-working fluids are increasingly causing OHP.<sup>2,8,16,42,43</sup> Other studies showed that contamination with micro-organisms (e.g. *Pseudomonas fluorescens*, mycobacteria, and fungi) could also be the cause of OHP in some cases.<sup>43-45</sup>

### Diagnosis

Despite valuable efforts by researchers, there are no definite diagnostic criteria for OHP.<sup>43</sup> Therefore, a detailed medical history and physical examination together with an occupational history are the most important steps to diagnose OHP. In addition, for definitive diagnosis, pathological confirmation is not always mandatory. Meanwhile, chest imaging, pulmonary function tests, bronchoalveolar lavage, and transbronchial lung biopsy may be helpful for diagnosis. Some tests are available to detect causative antigens, such as antigen-specific antibody titration, lymphocyte proliferation test (by antigen addition), the environmental challenge test, and precipitation antibody test. The antigen inhalation challenge test is valuable in antigen identification, and it may also detect OHP exacerbation. OHP should be differentiated from other interstitial lung diseases such as idiopathic interstitial pneumonitis, chronic obstructive pulmonary disease, and WRA.<sup>2,38</sup>

### Management and Prognosis

Avoiding exposure to causative factors is the first necessary step, even in under-treated patients, because the pathologic condition may progress. In mild cases, antigen avoidance may provide suitable prognosis, but in intermediate-to-severe, acute, or chronic cases, a corticosteroid prescription of prednisolone is used as a symptomatic therapy. The prognosis is poor in cases with continuous



antigen exposure or chronic fibrotic changes, with weak response to treatment.<sup>2,46</sup>

## Prevention

Complete elimination of the causative antigen in the workplace is mandatory; therefore, it is highly recommended that patients change to a safer work environment with fewer causative substances. Nevertheless, appropriate workplace ventilation and application of protective dust or gas masks may also be effective in exposure reduction. Furthermore, worker and employer education on OHP symptoms, avoidance of causative factors, protection methods, and so on may be beneficial.<sup>2</sup>

# OCCUPATIONAL SKIN ALLERGIES

## Definition and Classification

Skin exposure to workplace agents may result in immune mediated, non-immune mediated, and systemic effects.<sup>3</sup> Workplace-related skin diseases are defined under the general term of occupational skin diseases (OSD) which may be further classified into many categories, such as dermatitis, urticaria, different injuries, infection, insect bites, etc.<sup>2</sup> Occupational skin allergies (OSAs) including dermatitis and urticaria are OSDs due to immunologic reactions. In this way, occupational allergic dermatitis is defined as a local sensitisation reaction of the skin, based on an immunologic mechanism. On the other hand, occupational irritant dermatitis is a non-immunologic local reaction of skin as a result of exposure to workplace irritants. Similarly, urticaria, with apparent relation to workplace causative factors, is occupational.<sup>2</sup>

## Epidemiology

As the most frequent occupational disease, the estimated OSD annual costs exceed \$1 billion worldwide.<sup>47,48</sup> Because of direct or indirect contact of the widespread skin surface area with as many as 10,000 allergic agents, OSDs are commonly observed in different workplaces and occupations. Due to the differential nature of OSDs, epidemiologic studies are unable to provide accurate data and evaluation.<sup>2</sup> Recent studies indicated a decline in occupational dermatitis incidence in most European countries.<sup>47</sup> OSA prevalence is different in each sex but nonetheless accounts for nearly 90–95% of OSDs.<sup>3,47</sup> OSA is observed most commonly in personal service workers, including beauticians, hairdressers, and healthcare workers, as well as in food

processing industries, bread makers, chefs, agricultural workers, etc.<sup>2,47</sup>

## Causative Agents

Although the causative factors of OSAs are numerous, the most frequent are metals (nickel, chrome, etc.) and metal-working fluids, epoxy and acrylic resins, rubber, agrichemicals, cutting oil, cleansers, and some medications and plants. In addition, the main causative allergens of occupational urticaria include organic derivatives of food, plants, animals, wheat, crops, natural rubber products, etc.<sup>2,42,47</sup> On the other hand, chemical burns from acids, alkalis, hydrogen fluoride, cement, heating oil, etc. usually induce more severe types of acute irritant dermatitis.<sup>2</sup>

Proteins are frequently the causative allergen for recurrent allergic dermatitis, through different pathogenesis from Type IV allergic dermatitis, called occupational protein-contact dermatitis. Furthermore, some believe that hydrolysed wheat powder in soaps and shampoos may result in percutaneous-mucosal sensitisation and life-threatening wheat allergy. As an additive to cosmetics, foods, and drinks, the presence of the cochineal pigment may cause immediate acute allergy reactions.<sup>2</sup>

## Diagnosis

Occupational urticaria and dermatitis mostly occur on open skin areas i.e. hands, upper arms, and the face.<sup>2</sup> Diagnoses are based on accurate medical history, physical examination, and patch tests such as the simple closure test, open test, photopatch test, and repeated open application test. The patch tests evaluate the irritability of agents or identify the causative factors of allergic contact dermatitis.<sup>2,47</sup> To diagnose occupational urticaria, the prick test is highly sensitive and specific. The allergen-specific IgE may also be a useful criterion.<sup>2</sup> In recent times, it has been recommended to consider both skin and respiratory involvement in occupational allergic comorbidity.<sup>47</sup>

## Management

The identification and complete elimination or avoidance of the allergens and irritants is the most important priority in prevention and treatment. As the comorbidity of urticaria and dermatitis is presumable, it is required to alleviate the symptoms of both. Antihistamine prescriptions, topical or systemic steroids, immune suppressors, and ultraviolet phototherapy are useful treatments.

However, by eradication of the causative factor, the allergic dermatitis may be substantially cured.<sup>2</sup>

## Prevention

The primary prevention method is training, to improve the knowledge and awareness of workers and employers.<sup>47,49</sup> Meanwhile, the application of moisturising agents, barrier-creams, and non-allergenic gloves, masks, and clothes are recommended.<sup>2</sup>

## OCCUPATIONAL ANAPHYLAXIS

### Definition and Epidemiology

The occurrence or worsening of anaphylactic attacks due to workplace exposure to causative antigens is defined as occupational anaphylaxis (OAn).<sup>50</sup> The incidence rate of OAn is estimated to be 0.05–2% worldwide, and is thought to be increasing.<sup>2</sup>

### Diagnosis

Occasionally, late-onset anaphylaxis in the workplace may be caused by non-occupational allergens (ingestion-related) and should be differentiated from OAn, thus exact history-taking and clinical evaluation constitute an anaphylaxis diagnosis.<sup>50,51</sup>

### Causative Agents

Theoretically, every HMW and LMW allergen that triggers OA or urticaria may cause OAn. Natural rubber latex exposure and bee or wasp stings are the major causes of OAn, however workplace exposure to some medications, foods, insects, mammal and snake toxins, and chemicals are also notable.<sup>50,51</sup>

### Anaphylaxis by Bee or Wasp Stings

Anaphylaxis due to bee or wasp stings is seen mostly in apiculture, agriculture, forest, and landscaping industries, etc. Diagnosis is based mainly on medical and environmental history. The presence of atopy history in employees increases risk of bee or wasp anaphylaxis. Prevention can involve suitable protection tools. Similar to other anaphylaxes, adrenaline self-injection kits and antigen-specific immune therapy are effective treatments and should be prepared.<sup>50,51</sup>

### Anaphylaxis by Latex

Natural rubber latex is a derivative of the *Hevea brasiliensis* (rubber) tree.<sup>52</sup> Healthcare providers

and latex company workers are at risk of latex anaphylaxis so meticulous prevention of latex exposure is recommended. Accurate history-taking, identification of the specific IgE antibody, and the prick test may assist with diagnosis.<sup>50,51</sup> Furthermore, component-resolved diagnostics are valuable predictor tools.<sup>20,53</sup> Immediate allergic reactions to certain plant foods may occur in cases with latex allergy (known as latex fruit syndrome).<sup>2</sup>

### Management

Anaphylactic shock is a life-threatening emergency that requires in-place emergency guidelines, equipment, medications (including preloaded adrenaline), and trained individuals in workplaces.<sup>50,51</sup>

## CONCLUSION AND RECOMMENDATIONS

OAs are multidisciplinary diseases that impose a heavy burden on the healthcare system, economy, society, industries, and individuals worldwide. Close interaction and co-operation of allergists, occupational medicine specialists, immunologists, epidemiologists, social medicine specialists, internists, pulmonologists, and dermatologists, together with the support of social, industrial, and governmental authorities is mandatory to combat this group of conditions. Prevention and management of occupational allergies requires comprehensive guidelines for each of the diseases, and guidelines should be provided according to medical and occupational aspects. Furthermore, as occupational environments change over time, update classes should be scheduled at intervals. The guidelines must be easily available to workers and healthcare systems.

Employers are responsible for occupational hazards to their employees' health conditions, including allergic disorders, unless caused by the negligence of an employee. The employer should pay attention to their responsibilities, including prevention, cure, work cessation, compensation etc., if any occupational allergy threatens their employees. Additionally, insurance companies should be actively engaged in reduction of harm in the working environment for employees. They can help improve the implementation of preventive strategies and law execution in workplaces.

The establishment of a comprehensive occupational health surveillance system will provide valuable integrated information, which is useful for discovering new or known causative agents, detecting hazardous environments, and earlier

diagnosis. In general, the supportive and inspective role of legislation helps to decrease occupational injuries in the long-term. Particularly, the specific enforcement of regulations and laws to decrease environmental hazards will be more effective for employees, however it is not well-documented if penalties are useful.<sup>54</sup> General and specialised education of society, governors, workers, and managers should become mandatory, because it

is the first step in improving attitudes, knowledge, and practice toward the goal of an allergy-free occupational environment. Finally, comprehensive attention to these recommendations will be beneficial to human health and to maintenance of financial resources. These strategies could subsequently reduce the economic burden to the healthcare system.

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