



How should occupational anaphylaxis be investigated and managed?

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Purpose of review

Anaphylaxis is a systemic allergic reaction that can be life-threatening or fatal and can result from work-related exposures. This review study focuses on the assessment, main triggers, and management of occupational anaphylaxis.

Recent findings

Exposed workers can be sensitized through inhalation and skin contact, and the risks increase with penetration of the allergen through the skin. The main eliciting agents of occupational anaphylaxis include stinging insects and animal bites, natural rubber latex and other vegetable allergens, food products, and drugs. Workers sensitized to occupational allergens may also develop anaphylaxis outside the work environment from exposure to the same or to cross-reacting allergens. Cofactors at work such as exercise may increase the risk. The relevant medical records and laboratory tests (e.g. tryptase) performed during the episode should be reviewed.

Summary

It is very important to confirm the diagnosis and to identify the specific trigger of anaphylaxis. Component-resolved diagnosis may help in the identification of primary sensitizers or cross-reactive allergens. Adrenaline must be administered to all patients experiencing anaphylaxis. Removal from exposure is mandatory to prevent further episodes. A written emergency management plan, health and safety education, and training and surveillance should be enforced in occupations at greater risk.

Keywords

adrenaline, hypersensitivity reaction, occupational allergy, work-related agents

INTRODUCTION

There is no universal agreement on the definition of anaphylaxis and several definitions have been proposed by international allergy societies [1[•],2^{••},3^{••}]. All include the concepts of a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal [4^{••}]. The European Academy of Allergy and Clinical Immunology (EAACI) has endorsed the following operational definition [2^{••}]: anaphylaxis is a severe, systemic hypersensitivity reaction, which is characterized by being rapid in onset with life-threatening airway, breathing or circulatory problems and is usually, although not always, associated with skin and mucosal changes.

Recently, it has been emphasized that anaphylaxis can also arise from work-related triggering factors and elicitors [5[•]] and the term occupational anaphylaxis [6^{••}] has been coined. This review study focuses on the assessment, the main elicitors, and management of occupational anaphylaxis (OAn).

MECHANISMS AND ELICITING FACTORS

Mechanisms of OAn are similar to those of non-occupational anaphylaxis. An IgE-mediated allergic reaction is usually involved in the pathogenesis but in some instances an IgE-mediated mechanism has not been demonstrated, particularly when drugs or low-molecular-weight chemicals are the eliciting agents [2^{••},3^{••}].

Main triggers of OAn are insect stings/bites and natural rubber latex, food, medications, and similar triggers have been reported to cause nonoccupational anaphylaxis [5[•],6^{••}].

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KEY POINTS

- Relatively common triggering allergens of OAn include those from natural rubber latex and other vegetable products, stinging insects and other venoms, animals, food products, and medications.
- As with nonoccupational anaphylaxis, risks increase with penetration of the allergen through skin or mucous membranes, but anaphylaxis can also occur from inhalation exposure.
- Workers sensitized to occupational allergens may also develop anaphylaxis outside the work environment from exposure to the same or to cross-reacting allergens (e.g. HCW who are sensitized to natural rubber latex and develop anaphylaxis during dental procedures or from ingestion of cross-reacting fruits).
- Management includes removal of the implicated work allergen or a move for the worker to an unexposed area at the same or a different company.
- A written emergency management plan, health and safety education, and training and surveillance should be enforced in occupations at greater risk.

There are different scenarios in the development of anaphylaxis in occupational settings. Most commonly, patients may become sensitized to allergens present in the workplace and develop symptoms shortly upon exposure, usually after accidental inoculation, skin contact/penetration, inhalation, or animal stings/bites. On the other hand, the patient may be sensitized to cross-reacting allergens from foods or common aeroallergens (pollen, mites, etc.) and develop symptoms after occupational exposure because of allergenic cross-reactivity syndromes (pollen fruit/vegetable, fruits latex, mites shellfish, alpha-gal glycan-red meat). It may also occur that sensitization takes place at work, for instance to food or latex allergens, and anaphylactic reactions occur in nonoccupational environments after reexposure to the specific agent [5[•],6^{••}].

It is also worth remarking that physical activity at work can be a cofactor in the development of anaphylaxis, such as in food-dependent exercise-induced anaphylaxis syndromes, and can also be a sufficient trigger to elicit anaphylaxis by itself [6^{••}].

Hymenoptera venom allergy

Beekeepers, gardeners, farmers, truck drivers, masons, and forestry workers are the professionals most frequently affected by occupational venom allergy [6^{••}]. In fact, the frequency of hymenoptera venom allergy among these workers exceeds that expected among the general population. The type of

insect causing allergic reactions in outdoor workers may also differ from those in the nonoccupational setting. Bumblebee venom allergy is rare in the general population, and normally results from primary sensitization to bee venom. Notwithstanding, bumblebees are increasingly used for pollination of greenhouse plants and the increased use of this species has led to an increase in the frequency of adverse reactions to bumblebee venom [7]. Patients specifically sensitized to bumblebee generally work in greenhouses and are frequently stung.

Latex

Exposure to natural rubber latex (NRL) from *Hevea brasiliensis* constitutes an occupational hazard for workers in different sectors. Healthcare workers (HCWs) have been the most commonly affected, but other professions with exposure to latex products, such as cleaners, janitors, food handlers, hairdressers, and employees in NRL processing plants, among others, are also at risk of developing occupational allergy. The prevalence rate of sensitization to NRL among HCWs has been estimated between 2.9 and 12.1% [8^{••}].

Clinical manifestations of IgE-mediated allergy to latex proteins include contact urticaria, rhinitis, conjunctivitis, asthma, and anaphylaxis [8^{••}]. Reactions usually begin within minutes of exposure, and the clinical manifestations vary greatly depending on the route of exposure, the amount of allergen, degree of sensitization and other individual factors. An association between latex allergy and hypersensitivity to some plant foods, particularly fruits, has been established, which is called latex-fruit syndrome [9]. Banana, avocado, chestnut, and kiwi have been associated with anaphylaxis [8^{••},9].

Wheat allergens

Wheat-dependent exercise-induced anaphylaxis (WDEIA) usually develops after ingestion of wheat products followed by physical exercise or concurrence of other cofactors. The gliadins present in the salt-insoluble fraction of wheat flour, specifically omega-5 gliadin, and high-molecular-weight glutenin subunits are the main allergens involved in this condition [10^{••}].

An increased incidence of a new subtype of WDEIA, which is likely to be because of sensitization via percutaneous and/or rhinoconjunctival route to hydrolyzed wheat protein (HWP) contained in soap and cosmetic products, has been recently described [11]. In these patients, contact allergy with soap exposure usually preceded wheat ingestion-induced reactions. The predominant observed symptom of

the new WDEIA subtype was angioedema of the eyelids; a number of patients developed anaphylaxis. This new subtype of WDEIA has little omega-5 gliadin-specific serum IgE [11]. An epidemiological relationship between wheat allergy and contact exposure to HWP has been documented [12]. This finding implicates a possible role of contact exposure to food-derived protein hydrolysates as a risk factor for the development of food allergy manifesting as anaphylaxis. It has been recently reported that hairdressers may develop occupational allergy to HWP (rhinitis, asthma, and contact urticaria) followed by WDEIA [13].

Animal bites

Workers exposed to laboratory animals may experience systemic symptoms and anaphylaxis, especially after rodent bites. Anaphylactic reactions have been reported among laboratory animal handlers, technicians, and researchers after rat [14] or dwarf hamster bites [15]. Exposure to rabbit tissue allergens has been reported to elicit anaphylaxis after a needle injury in a research physician [16].

Horse allergy is induced by exposure to the major horse allergens Equ 1 through 5. Greatest risk of anaphylaxis occurs in sensitized patients who have large amounts of animal allergen exposure, such as in a barn or when a horse bite exposes sensitized persons to large quantities of the animal allergens present in the saliva [17,18[¶]].

Herpetologists and snake farm workers are at risk of anaphylaxis because of handling of venom and snakebites [19]. Aerosolized snake venom has been considered a potential source of allergens that may result in anaphylaxis on subsequent exposure [20]. Anaphylaxis and serum sickness to antivenom are a risk, particularly to workers with vipers (*Bothrops moojeni*) who were bitten more than once [21]. Several allergens in different viper snake venoms have been characterized and identified as a phospholipase and metalloproteinases [22].

Medications

Sensitization to drugs can take place in the workplace either through topical contact with spilled drugs or by inhalation of powder or foam. Drugs are one of the most common causes of allergic diseases in HCWs, including nurses and pharmacists, as well as people employed in the manufacturing process. The increased rate of sensitization to drugs among healthcare personnel is because of regular contact with the relevant allergens.

Occupational allergic diseases caused by these agents commonly include exacerbations of asthma,

upper airway symptoms, and contact dermatitis. Although anaphylaxis is less frequent, there is often a history of milder self-limiting reactions prior to its development. Anaphylaxis can take place in the workplace; however, it may also happen when the sensitized worker receives the implicated medication as a patient [23].

The commonest class of drugs associated with OAn is the β -lactam antibiotics; the sensitization rate of cephalosporin may be lower than that of penicillin [24]. There have been cases of anaphylaxis to other β -lactam antibiotics as piperacillin [25].

Other classes of drugs have also been identified as causing occupational anaphylaxis. HCW can develop IgE-mediated allergy to chlorhexidine. Although initial symptoms may be mild, chlorhexidine allergy carries a risk of anaphylaxis [26].

Psyllium was frequently reported as a cause of occupational allergy until the powdered form was changed to granules [27], and there have been single case reports of OAn in an anaesthetist to neuromuscular blocking drugs [28].

DIAGNOSIS OF ANAPHYLAXIS

The diagnosis of anaphylaxis is based primarily upon clinical symptoms and signs, as well as a detailed description of the acute episode, including antecedent activities and events occurring within the preceding minutes to hours. Anaphylaxis is not always easy to recognize clinically since there are no pathognomonic signs or symptoms [29–30].

The clinical manifestations of anaphylaxis depend on the organ systems involved. Diagnostic criteria for anaphylaxis were initially published by a multidisciplinary group of experts [31], and these were subsequently endorsed by EAACI [2^{¶¶}]. It was acknowledged that no criteria will provide 100% sensitivity and specificity, but using these criteria is estimated to diagnose approximately 95% of anaphylaxis. Anaphylaxis is highly likely when any one of the following three criteria is fulfilled.

Criterion 1

Acute onset of an illness (minutes to several hours) involving the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) and at least one of the following:

- (1) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, and hypoxemia).
- (2) Reduced blood pressure or associated symptoms and signs of end-organ dysfunction [e.g. hypotonia (collapse) syncope and incontinence].

Criterion 2

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- (1) Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, and swollen lips-tongue-uvula).
- (2) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, and hypoxemia).
- (3) Reduced blood pressure or associated symptoms and signs [e.g. hypotonia (collapse), syncope, and incontinence].
- (4) Persistent gastrointestinal symptoms and signs (e.g. crampy abdominal pain and vomiting).

Criterion 3

This criterion mentions the reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours). Once the diagnosis of anaphylaxis has been established, the diagnosis of OAn is made if the causative role of a specific workplace agent can be demonstrated.

RISK OF SEVERE ALLERGIC REACTIONS

The severity of anaphylaxis is related to the speed of progression of symptoms, the type of antigen and its pathway, and the organs affected [32]. Old age, combined with comorbidities such as cardiovascular disease and preexisting lung disease appear to be the major determinants for severe anaphylaxis. β -adrenergic blocking agents also have been reported to be associated with more severe events and can interfere with the activity of epinephrine [3^{''}].

Patients with mastocytosis or mast cell activating syndromes are at increased risk for anaphylaxis and have been associated with severe reactions and increased mortality. These conditions should be suspected in patients with recurrent anaphylaxis who present with cardiovascular symptoms in the absence of urticaria or angioedema. The scoring model proposed as a screening tool in patients presenting with anaphylaxis in the absence of skin mastocytosis may be useful [33].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anaphylaxis includes medical diseases which affect the organ systems most frequently involved in anaphylaxis: urticaria/angioedema, flushing syndromes, other forms of shock, vocal cord dysfunction syndrome, and

postprandial syndromes [3^{''}]. The most common condition mimicking anaphylaxis is the vasovagal reaction; the characteristic bradycardia and the fact that these reactions are not accompanied by cutaneous manifestations, such as urticaria, angioedema, or flush are the most important distinguishing factors. However, it should be noted that bradycardia can occur during anaphylaxis, but in this case tachycardia often precedes the onset of bradycardia [3^{''}].

Laboratory findings

Laboratory tests are not helpful in diagnosing anaphylaxis at the time of patient presentation. Retrospectively, the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction when compared with the patient's baseline levels, however tryptase levels within the normal reference range do not rule out anaphylaxis [3^{''},34].

Allergologic work-up

Any patient with a history of anaphylaxis should be considered for referral to an allergy specialist. The clinical and occupational history is the most important tool to determine whether a patient has had anaphylaxis and to ascertain whether an occupational substance was the eliciting agent of the episode [6^{''}].

Evidence of IgE sensitization by skin tests (prick tests/intradermal test) or in-vitro testing is an important aid in the diagnosis [4^{''},6^{''}]. However, for many occupational allergens there are no commercially available test allergens and skin testing with raw and home-made materials should be carried out carefully. Measurement of specific IgE antibody using standardized test systems is not available for many potential work-related allergens [6^{''}]. Component-resolved diagnosis can improve the diagnostic efficiency [35^{''}].

Challenge tests may be required if diagnostic doubt remains and are the only method to verify hypersensitivity to nonallergic elicitors. As they are potentially dangerous, they should be undertaken only if their outcome is required to clarify a clinically important question [6^{''}].

MANAGEMENT OF ANAPHYLAXIS**At the workplace**

Removal of the trigger and call for help: the likely trigger of the anaphylaxis should be immediately removed, if possible, and help should be called from the emergency medical services. If adrenaline is

available, this should be administered while awaiting emergency services [6²²].

Emergency management of anaphylaxis

As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing, and circulation. Deaths result from upper airway, lower respiratory, and/or cardiovascular compromise so emergency management must focus on these manifestations [2²²–4²²].

Adrenaline

International guidelines concur that adrenaline is the first choice medication in the treatment of anaphylaxis. Adrenaline must be administered to all patients experiencing anaphylaxis; the dose and route depend on the severity of the reaction. In almost all office management situations, the vastus lateralis muscle is the site of choice [4²²,36]. If severe hypotension is present, adrenaline can be administered intravenously (adrenaline 1 mg in saline 1000 ml) [2²²].

Oxygen

High-flow oxygen should be administered by face mask to all patients with anaphylaxis.

Positioning of the patient

Patients experiencing anaphylaxis should be placed in a recumbent position with the lower extremities elevated unless precluded by shortness of breath or vomiting.

Inhaled short-acting β -2 agonists

Inhaled short-acting β -2 agonists can be additionally given to relieve symptoms of bronchoconstriction in patients with anaphylaxis.

Fluid support

Intravenous fluids should be administered to patients with cardiovascular instability, as adrenaline may not be effective without restoring the circulatory volume.

H1 and H2-antihistamines

Systemic antihistamines are commonly used in anaphylaxis but have only been demonstrated to relieve cutaneous symptoms and should be considered a second-line treatment for anaphylaxis.

Glucocorticosteroids

Oral or intravenous glucocorticosteroids are commonly used in anaphylaxis and are thought to

possibly prevent protracted anaphylaxis symptoms and also biphasic reactions. Because the onset of action is slow, steroids are not useful in the acute management stage.

Glucagon

Parenteral administration of glucagon may be useful in treating patients with anaphylaxis who are unresponsive to adrenaline, particularly in those taking β -blockers.

Monitoring and discharge arrangements

Before discharge, the risk of future reactions should be assessed and an adrenaline auto-injector prescribed to those at risk of recurrence, and the workers should be referred to an allergy specialist to investigate possible triggers [2²²].

Long-term management of anaphylaxis

The long-term management of patients who have experienced anaphylaxis starts with the identification and elimination of triggering allergens. Preventive strategies to avoid recurrence include allergen avoidance and allergen immunotherapy (with hymenoptera venom for those with anaphylaxis to stinging insects) should be implemented [2²²,3²²,31]. Reduction of exposure tends to reduce initial sensitization and consequently anaphylactic reactions [5²²].

Prevention strategies to avoid recurrence in workers who have experienced anaphylaxis should be established. Those who have had serious adverse reactions should be carefully instructed about hidden allergens, cross-reactions to other allergens, provided with an emergency kit with an anaphylaxis action plan and medications for self-treatment (including a preloaded epinephrine injector), and wear Medic-Alert bracelets [3²²,6²²].

Management of NRL allergic patients includes avoiding latex-containing products and symptomatic medication when needed. Personnel sensitized to latex must avoid all direct contact with latex-containing products. Avoidance measures also require the use of nonpowdered and nonallergenic gloves by workmates and the replacement of all material containing latex [8²²].

In the primary and secondary prevention of hypersensitivity reactions to insect stings, reduction of exposure is recommended [37]. Education of employees, how to prevent stings, should be part of the safety provisions for outdoor workers. For highly exposed employees, protective clothing with nets should be routine, at least during hazardous activities. Workers with insect venom anaphylaxis

Table 1. Steps in the evaluation of occupational anaphylaxis [6^{***}]

Detailed history of the episode focusing on the antecedent clinical symptoms and signs and obtain information from fellow workers
Review the relevant medical records (e.g. ambulance, occupational health clinic, etc.) and laboratory tests (e.g. serum tryptase) performed during the episode
Review the differential diagnosis, which commonly includes hives, asthma, anxiety/panic attack, fainting, and choking
Carefully review the history of the episode and enquire about potential inhalational and ingestion-related triggers
Investigate for concomitant diagnoses such as asthma and cardiovascular diseases, as well as concurrent medications such as β -blockers and ACE inhibitors
Perform relevant skin tests – skin prick tests (SPTs) for foods or other agents (e.g. latex) and intradermal tests for insect venoms or β -lactam antibiotics
Perform allergen serum specific IgE quantitative measurements. Challenge tests should be undertaken only if their outcome is required to clarify a clinically important question
Other assessments such as workplace industrial hygiene measurements may prove useful in certain contexts

should not work on ladders or at heights because of the increased risk of loss of consciousness associated with a sting.

Venom immunotherapy can be 95 to 100% effective in preventing systemic reactions to stings [37]. The standard recommended dose of 100 μ g of each venom was originally selected to be equivalent to the estimated venom protein content of two to four stings. The amount of venom protein injected by a honeybee sting is consistently in the range of 50 μ g, but there is considerable variability in the amount of venom injected by the vespids, with estimates of 2 to 20 μ g/sting. The efficacy of the 100- μ g dose has contributed to its widespread acceptance. Patients with bee venom allergy and an intense exposure should be treated with an increased maintenance dose of 200 μ g venom. Venom immunotherapy should be continued for the duration of the hazardous occupation and efficacy of venom immunotherapy should be demonstrated before allowing the patient to return to his/her occupation [6^{***}]. For patients allergic to bumblebee venom, since they show scarce cross-reactivity with bee venom, the use of bumblebee venom for immunotherapy is recommended [7,37]. The main steps in the evaluation of OAn are shown in Table 1 [6^{***}].

CONCLUSION

Anaphylaxis is a severe and potentially life-threatening systemic allergic response that can be elicited by agents present at the workplace. The mechanisms involved are similar to those of nonoccupational anaphylaxis. Cofactors at work, particularly exercise, may increase the risk of developing this clinical emergency. In the evaluation of OAn it is very important to confirm the diagnosis and to identify the anaphylaxis trigger. Treatment of the acute episode is the same as for nonoccupational anaphylaxis, and long-term management implies strict

avoidance of eliciting agents and removal from exposure.

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Conflicts of interest

There are no conflicts of interest.

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