

Anaphylaxis in the Workplace

Darío Antolín-Amérigo, M.D., Ph.D.^{1,*}

Alberto Alvarez-Perea, M.D., Ph.D.^{2,3}

Ana Fiandor, M.D., Ph.D.⁴

Address

^{1,*}Servicio de Enfermedades del Sistema Inmune-Alergia, Departamento de Medicina y Especialidades Médicas, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá (IRYCIS), Carretera de Alcalá-Meco s/n. 28085, Alcalá de Henares, Madrid, Spain

Email: dario.antolin@gmail.com

²Allergy Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain

³Gregorio Marañón Health Research Institute, Madrid, Spain

⁴Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

Published online: 22 January 2018

© Springer International Publishing AG, part of Springer Nature 2018

This article is part of the Topical Collection on *Occupational Allergy*

Keywords Anaphylaxis · Occupational diseases · Epinephrine · Hypersensitivity · Allergy · Environment

Abstract

Occupational anaphylaxis (OcAn) main causes comprise food, medications, insect stings/bites, and natural rubber latex (NRL). An in-depth investigation is required, before labeling a reaction as OcAn.

A written emergency management plan, health and safety education, and training and surveillance should be implemented after proper diagnosis. Education on when and how to use the adrenaline auto-injector device should be provided likewise. Moreover, surveillance and advice on risk of allergen exposure and how to minimize their risk of sensitization at the beginning of their employment or training is mandatory. Workers who have developed sensitization to an allergen in the occupational setting may also develop anaphylaxis outside the work environment, from exposure to the same or to cross-reacting allergens. We believe that removal from exposure shall avoid subsequent OcAn episodes; therefore, once OcAn has been diagnosed, this intervention shall be implemented.

This review highlights the different causes of OcAn, their physiopathology, cofactors, diagnosis, and its management, focusing on the medication spectrum. Interested readers may acquire knowledge on this severe, potentially life-threatening systemic hypersensitivity reaction, which generally involves an immunologic IgE mechanism.

Introduction

EAACI Guidelines consider anaphylaxis as a clinical emergency whose management is crucial. It is defined as a severe, potentially life-threatening systemic

hypersensitivity reaction, characterized by a rapid onset of airway, breathing, circulatory, or gastrointestinal problems, which is usually but not always associated

with skin and mucosal changes [1]. Its physiopathology generally involves an immunologic IgE mechanism, but IgE-independent immunologic mechanisms and direct mast cell stimulation are also involved as pathophysiological events in anaphylaxis [2••].

Anaphylaxis can also arise from work-related triggering factors and elicitors and the term occupational anaphylaxis (OcAn) has been coined. It could be defined as anaphylaxis arising out of triggers and conditions attributable to a particular work environment [3, 4].

OcAn main causes comprise food, medications, insect stings/bites, and natural rubber latex (NRL) [5].

Although the clinical manifestations of OcAn shall depend on the organ systems involved, its symptoms and signs show a rapid onset, generally within 2 h of exposure to the allergen [6], time lapse which is regularly shorter for food allergy, and parenteral medication or insect stings [7].

The triggers of occupational anaphylaxis may come into contact with the individual by inhalation or skin contact (mainly, in a person with preexisting skin disease), by injection through stings or bites, or following hand-to-mouth transmission. Any workplace agent capable of causing occupational asthma or generalized urticaria may theoretically cause anaphylaxis [3]. Therefore, occupational exposures may vary from non-occupational ones, in terms of intensity and route of exposure [4].

In any case, the recommendation of the EAACI OcAn task force is removal from exposure, to prevent further episodes [4].

A written emergency management plan, health and safety education, and training and surveillance should be implemented. Education on when and how to use the adrenaline auto-injector device should be provided.

Mechanisms

Mechanisms of OcAn are similar to those of non-occupational anaphylaxis [8].

Workers who have developed sensitization to an allergen in the occupational setting may also develop anaphylaxis outside the work environment, from exposure to the same or to cross-reacting allergens [4]. On the contrary, a reaction that occurs in the workplace can also be the result of a cross-reaction between a non-occupational allergen, to which the patient is sensitized, and an occupational allergen. Consequently, an in-depth investigation is required, before labeling a reaction as OcAn.

Exposed workers can be sensitized through inhalation and skin contact and by injection through stings or bites. Any workplace agent capable of causing occupational asthma or generalized urticaria may theoretically cause anaphylaxis. Cofactors at work such as exercise may increase the risk.

The main eliciting allergens include food, medications, insect stings/bites, natural rubber latex (NRL), and other vegetable allergens (Table 1). Both high-molecular-weight and low-molecular-weight agents have been described as cause of occupational anaphylaxis [3].

Specific causes of occupational anaphylaxis

Foods

Occupational exposure to foods usually leads to contact dermatitis, urticaria, and respiratory symptoms, albeit anaphylaxis is the most serious consequence of food allergy.

Although in workers handling seafood, the prevalence of occupational asthma and contact dermatitis ranges from 7 to 36% and 3 to 11%, respectively [9], OcAn has been described in a few case reports only [4]. Hence, there is

Table 1. Triggers of occupational anaphylaxis

Trigger		Occupations
Foods		Food processing plants, seafood deliveries, cooks, bakers
Medications		Healthcare workers, manufacturing process workers
Arthropods	Hymenoptera	Beekeepers, gardeners, farmers, truck drivers, masons, greenhouse workers
	Ticks	Goatherds, shepherds, livestock farmers, building maintenance workers, gardeners
	Pine processionary caterpillars	Pinecone or resin collectors, woodcutters, farmers, stockbreeders
	Chironomid larvae	Aquarists
Mammals	Rodents	Scientists, technicians, physicians, animal handlers
	Horses	Stockbreeders, farmers, veterinaries
Reptiles	Snakes	Herpetologists, snake farm workers, zoo or reptile park workers, researchers
Natural rubber latex	Healthcare workers, rubber industry workers, researchers	Hairdressers, beauticians, ceramists, nurses, technicians
Chemicals	Dyes, bleaches, low-molecular-weight agents (LMW), cobalt chloride, diphenylmethane diisocyanate, methylmethacrylate, benzonitrile, fragrances, and HBTU	

a prominent discrepancy between reported prevalence of work-related skin and respiratory disorders and the scant data on OcAn to food allergens [4].

An unnoticed occupational sensitization to a food allergen can lead to systemic and anaphylactic reactions in a non-occupational environment after consumption of the culprit food allergen. Anaphylaxis after ingestion of spices, mustard [10], buckwheat [11], seafood [12], and egg [13, 14] has been reported.

Wheat allergens

Wheat-dependent exercise-induced anaphylaxis (WDEIA), as a specific subtype of food-dependent, exercise-induced anaphylaxis (FDEIA), usually develops after ingestion of wheat products followed by physical exercise or concurrence of other cofactors [8]. Furthermore, as it has been recently stated, exercise is not essential for the development of symptoms, and that if enough of the culprit food is ingested, often with additional augmentation factors, such as alcohol or non-steroidal anti-inflammatory drugs (NSAIDs), symptoms can be induced at rest in the challenge setting [15••, 16].

The gliadins present in the salt-insoluble fraction of wheat flour, specifically omega-5 gliadin (water insoluble but ethanol soluble), and high-molecular-weight glutenin subunits are the principal allergens involved in this entity [17].

Sensitization via percutaneous and/or rhinoconjunctival route to hydrolyzed wheat protein contained in soap and cosmetic products has been recently described in Japanese women [8, 18]. Of note, omega-5 gliadin is not the main allergen in this variant of WDEIA [8, 19]. Moreover, hairdressers may develop occupational allergy to hydrolyzed wheat protein (HWP), as it is a common ingredient in food and cosmetic products [20].

Medications

Sensitization to drugs can occur in the workplace either through topical contact with spilled drugs or by inhalation of powder or foam [4]. Drugs are one of the most common causes of allergic diseases in healthcare workers, including physicians, nurses, and pharmacists, as well as people employed in the manufacturing process.

While anaphylaxis is uncommon, there is often a history of milder self-limiting reactions, such as exacerbations of asthma, upper airway symptoms, and contact dermatitis prior to its development [8]. Anaphylaxis can take place in the workplace; however, it may also happen when the sensitized worker receives the implicated medication as a patient [21, 22].

Risk factors comprise those associated with individuals, as well as the factors relating to the drug that they are being exposed to such as β -lactam antibiotics which have been historically frequent sensitizers. However, the incidence is now significantly lower as most preparations do not require substantial preparation with aerosolization of product, as they are in single-dose packaging. Several factors are predisposing and leading to increased risk, such as preexisting hand dermatitis, a history of atopy, repeated exposure, and duration of employment [23••]. Natural and semisynthetic penicillins used to be the drugs most commonly associated with occupational anaphylaxis. Notwithstanding, as their use declines and cephalosporin use grows, so does occupational allergy to cephalosporins. Some studies have described up to 17% of healthcare workers' present sensitization to cephalosporins [23••]. Other beta-lactam antibiotics as piperacillin have also been reported as cause of occupational anaphylaxis [24].

Other classes of drugs have also been reported as causing occupational anaphylaxis. Healthcare workers can develop IgE-mediated allergy to chlorhexidine, psyllium, neuromuscular blocking agents, and allergen immunotherapy [25–28].

Animals

Arthropods

Hymenoptera venom allergy

Beekeepers, gardeners, farmers, truck drivers, masons, and forestry workers are the professionals most frequently affected by occupational venom allergy [4]. As a matter of fact, the frequency of Hymenoptera venom allergy among these workers exceeds that expected among the general population [4]. Hymenoptera stings during work activities are specifically recognized as an occupational risk for beekeepers, but other outdoor workers appeared to share the same or similar occupational risks [29].

The type of insect causing allergic reactions in outdoor workers may also differ from those in the non-occupational setting. It has been reported that insects belonging to genera *Bombus* (e.g., bumblebees), *Dolichovespula*, *Polistes*, or *Vespa* usually do not collect food at anthropogenic sources [4]. Insects belonging to the genus *Bombus* are generally less aggressive and stings by these insects occur very seldom in the general population. However, the growing use of bumblebees for pollination of greenhouse plants has led to an increase in the frequency of adverse reactions to bumblebee venom among greenhouse workers [4, 30].

To prevent hypersensitivity reactions to insect stings, reduction of exposure is recommended. Education of outdoor workers should include information on how to prevent stings. Detailed information should be provided to subjects at risk, about where the culprit insect builds its nest, as well as the types of food which attract it. For highly exposed employees, protective clothing with nets should be routine, at least during hazardous activities, for example, for beekeepers who work in or closely to beehives and for gardeners who work near wasp nests. Workers with insect venom anaphylaxis should not work with the relevant stinging insects or outdoors in areas where they are more likely to be stung and particularly should not work on ladders or at heights due to the increased risk of loss of consciousness associated with a sting [31, 32, 33•].

Non-hymenoptera

Tick bites have been reported as elicitors of anaphylactic reactions especially during occupational or recreational exposure. Specific IgE antibodies have been demonstrated to *Ixodes holocyclus*, *I. ricinus*, *I. pacificus*, *Rhiphicephalus* sp., and *Argas reflexus*. Goatherds, shepherds, livestock farmers, building maintenance workers, and gardeners are the professionals most frequently affected [4, 34, 35].

In a recent cross-sectional study performed in Germany, forest service employees and hunters showed a high prevalence of alpha-gal-sIgE positivity and pose a considerable risk of red meat allergy. The odds ratio for alpha-gal-sIgE positivity in forest service employees and hunters was 2.48 compared to the residential population [36•].

The pine processionary caterpillar *Thaumetopoea pityocampa* is a frequent cause of contact urticaria and angioedema by nonallergic (mechanical, irritant) mechanisms, although IgE-mediated anaphylactic reactions have been described [37]. Recently, a case of occupational IgE-mediated severe anaphylaxis in a pine-resin worker attributable to pine processionary caterpillar as the clinical presentation of an underlying indolent systemic mastocytosis without skin lesions has been reported [38]. Pinecone or resin collectors, woodcutters, farmers, and stockbreeders are the most frequently and severely affected workers.

Other insect-derived allergens implicated in anaphylactic reactions are *Chironomidae* larvae used by aquarists as fish food. *Chironomidae* and aquarium fish food arthropods as freshwater shrimp (*Gammarus* specie) are potent allergens with an elevated prevalence of sensitization and variable degree of cross-reactivity [39].

Mammals

Laboratory animal workers such as scientists, technicians, physicians, and animal handlers are at an increased risk of sensitization and allergy to animals in their workplace and may develop allergic respiratory symptoms and contact urticaria [4]. Rodents, in particular rats and mice, are the most important laboratory animals that contribute to occupational anaphylaxis because of their widespread use in experimental research. 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, mice [40, 41], or dwarf hamster bites [42]. Moreover, exposure to rabbit tissue allergens has been reported to elicit anaphylaxis after a needle injury in a research physician [43].

Most of the major mouse and rat allergens are produced in the liver under the influence of androgenic hormones. Therefore, working with male rodents is an important risk factor for the development of laboratory animal allergies [41].

In terms of horse allergy, 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 [4, 44, 45].

Animal workers should receive education about the risk of allergen exposure and how to minimize their risk of sensitization at the beginning of their employment or training [46].

Snakes

Herpetologists, snake farm workers, zoo or reptile park workers, and researchers on snakes are at higher risk of anaphylaxis due to handling of venom and snakebites [4, 8, 47].

Hypersensitivity to snake venom is uncommon but can be an underdiagnosed circumstance leading to fatal snake biting injury in sensitive patients, independently from the toxicity of the venom [8]. Hypersensitivity to snakebites has been described in individuals who have had repeated snakebites from the same or related species and, presumably, through repeated inhalation of or dermal/mucosal contact with dry or aerosolized snake venom [48, 49].

Several allergens in viper snake venom have been characterized and identified as phospholipase, venom serine proteinases, and metalloproteinases [8, 48, 49]. Recently, crotoxin (phospholipase A2) has been identified as an allergen to cause occupational anaphylaxis in a researcher [50].

Latex (NRL)

Exposure to natural rubber latex (NRL) from *Hevea brasiliensis* constitutes an occupational hazard for workers in different sectors, such as healthcare workers (HCWs), cleaners, janitors, food handlers, hairdressers, and employees in NRL-processing plants [4, 8]. The prevalence rate of sensitization to NRL among HCWs has been estimated between 2.9 and 12.1% [51•]. Powder inhalation seems to be more relevant in factory workers, whereas a double effect of inhalation of latex protein-coated glove powder with the high skin exposure appears to be predominant in healthcare workers [51•, 52•]. Clinical manifestations of IgE-mediated allergy to latex proteins include contact urticaria,

rhinitis, conjunctivitis, asthma, and anaphylaxis [51•]. 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 [53]. Banana, avocado, chestnut, and kiwi have been associated with anaphylaxis [51•, 52•, 53]. Component-resolved diagnosis has proven useful to enhance the diagnosis of NRL allergy. In HCWs suffering from occupational NRL allergy, the most relevant allergens are Hev b 5 and Hev 6.01 or Hev b 6.02. While Hev b 1 and Hev b 3 are often recognized by spina bifida patients, they are minor allergens in HCW [54].

Subjects sensitized at work may also have increased risk in a non-occupational setting, during medical/surgical procedures when others wear NRL gloves or use catheters, etc. Anaphylaxis has occurred in both the occupational setting (e.g., in an operating room nurse) [55] and following occupational sensitization to NRL, during health care (e.g., a radiologist during a personal barium enema procedure [56]. Nevertheless, the introduction of powder-free latex gloves and synthetic gloves (latex-free) has been very successful in lowering the prevalence of sensitization and allergy to latex [57].

Chemicals

Dyes and bleach

Oxidative hair and leather dyes and temporary henna tattoos contain paraphenylenediamine (PPD), which is a strongly sensitizing aromatic amine [58]. Severe skin and respiratory symptoms and anaphylaxis to PPD [59] and other hair dyes [60] as well as to ammonium persulfate present in hair bleaches [61] have been reported. Workers who manipulate these chemicals may suffer from reactions outside their workplace, such as a case of a hairdresser who had allergy to persulphates obtained during professional work, who developed anaphylaxis caused by persulphates present in dental cement during dental treatment [61]. On the contrary, reactive textile dyes are a common cause of IgE-mediated occupational asthma and exceptionally may give rise to anaphylaxis after inhalation [62].

Other chemicals

Miscellaneous agents may induce systemic symptoms and/or anaphylaxis by unknown mechanisms. Causative agents include low-molecular-weight agents (LMW) [63], cobalt chloride [64], diphenylmethane diisocyanate [65], methylmethacrylate [66], benzonitrile [67], fragrances [68], and HBTU [69].

Diagnosis

The diagnosis of occupational anaphylaxis requires confirmation of the diagnosis of anaphylaxis. Furthermore, it is important to make an effort to identify the

causative agent in the workplace, as this has major implications for secondary and tertiary prevention including removal from exposure and relocation [4].

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. In addition, it is very important to investigate concomitant individual risk factors, such as diagnoses of asthma and/or cardiovascular disease, concurrent medications, such as beta-blockers and angiotensin-converting enzyme inhibitors, and possible mastocytosis or mast cell activation disorders. Moreover, it is important to consider that biphasic anaphylactic reactions may pose up to a 20% of reactions [1].

Patients with mast cell disorders are at increased risk for anaphylaxis and have been associated with severe reactions and increased mortality. The REMA Score model proposed as a screening tool in patients presenting with anaphylaxis in the absence of skin mastocytosis has shown its convenience [70].

Anaphylaxis is not always easy to recognize clinically since there are no pathognomonic signs or symptoms, and it is commonly underdiagnosed, being its incidence even double that estimated in the emergency department [8, 71••]. It may be mild and may disappear spontaneously or it may be severe and progress within minutes to respiratory or cardiovascular compromise and death. Anaphylaxis may be difficult to recognize if it is triggered by a novel agent and if it is an individual's first episode as when skin signs such as urticaria are absent or masked by medications [1, 4, 8, 71••]. 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 [72]. Notwithstanding, it is necessary to improve resources related to the diagnosis and management of anaphylaxis in some countries [73].

Diagnostic criteria for anaphylaxis are not universally accepted. The most widely used clinical criteria are those of the NIAID/FAAN consensus, which was based on the opinion of representatives of a number of international allergy organizations [74]. These criteria have been validated retrospectively [75] and prospectively [76], demonstrating high sensitivity and negative predictive value, which makes them useful for the diagnosis of anaphylaxis (Table 2).

Once the diagnosis of anaphylaxis has been established, the diagnosis of OcAn is made if the causative role of a specific workplace agent can be demonstrated [8].

After an episode of anaphylaxis, all patients should be advised that their specific anaphylaxis triggers need to be confirmed by an allergy specialist. Important differences between the etiological diagnosis suspected during the acute event and the confirmed cause of anaphylaxis have been reported in recent studies [71••, 77, 78]. Upon trigger identification, patients will also be provided with information on possible cross-reacting agents and alternatives. This has demonstrated useful to reduce the risk of severe anaphylaxis [79].

Confirmation of sensitization to the allergen is traditionally performed by using skin prick tests or intradermal tests, optimally performed under controlled conditions at least 3 to 4 weeks after the anaphylaxis episode. However, for many occupational allergens, there are no commercially available test allergens. Skin testing with raw and home-made materials should be carried out with caution. The interpretation of positive skin tests to nonstandardized substances has to be done with care.

Table 2. Diagnostic criteria for anaphylaxis, adapted from [74]**Diagnostic criteria for anaphylaxis**

Anaphylaxis is highly likely when any *one* of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula, and at least one of the following):
 - a. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a *likely* allergen for that patient (minutes to several hours):
 - a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch–flush, swollen lips–tongue–uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known* allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP*
 - b. Adults: systolic BP of < 90 mmHg or > 30% decrease from that person’s baseline

PEF peak expiratory flow, BP blood pressure

*Low systolic blood pressure for children is defined as < 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2–9 age]) from 1 to 10 years, and < 90 mmHg from 11 to 17 years

In vitro tests for measurement of allergen-specific IgE are now widely available in clinical laboratories for many allergens, including foods, stinging insect venoms, natural rubber latex, and the majority of medications. Quantitative tests such as ImmunoCAP (ThermoFisher Scientific), Immulite (Siemens Healthineers), and others are the preferred tests for in vitro use. However, for many potential work-related allergens, standardized tests are not available or are often of poor quality due to poor sensitivity/specificity. Multiallergen IgE immunoblotting and component-resolved diagnosis should improve the diagnostic efficiency [80–82].

Challenge tests such as specific inhalation challenge using the suspected product may confirm clinical relevance of a sensitization to an allergen 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. All precautions to minimize the patient’s risk should be taken, and challenge tests should only be performed by clinicians with expertise [2••, 4, 83].

A diagnostic algorithm is proposed (Fig. 1) and the steps in the evaluation of OcAn are shown in Fig. 2.

Cofactors

Cofactors increase the risk of an allergic reaction occurring or its severity [2••]. They have been described in nearly 20% of young patients in a prospective registry study [84] and include exercise, fever, acute infection, premenstrual

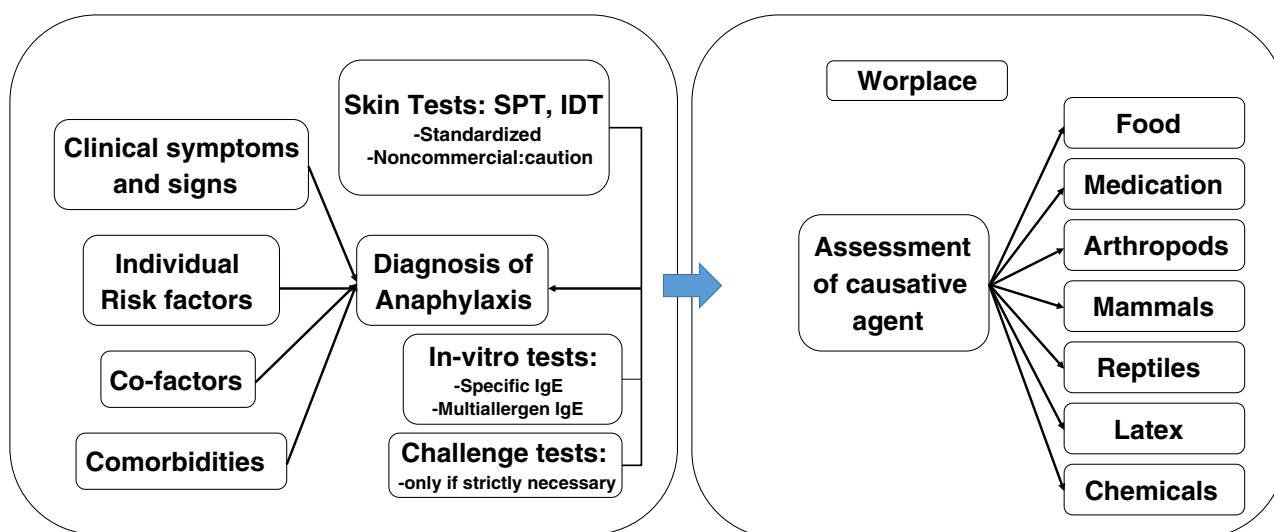


Fig. 1. Proposed diagnostic algorithm of occupational anaphylaxis.

status, and emotional stress. NSAID and alcohol intake also seem to enhance some food-allergic reactions [1]. Exercise-induced anaphylaxis (EIA) and food-dependent, exercise-induced anaphylaxis (FDEIA) are more often seen in adults than in children. The association with exercise is crucial for the onset of symptoms or signs [85]. The range of triggering physical activities and intensities is broad. EIA is not fully reproducible so that same exercise may not always result in anaphylaxis in a given patient.

Differential diagnosis

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

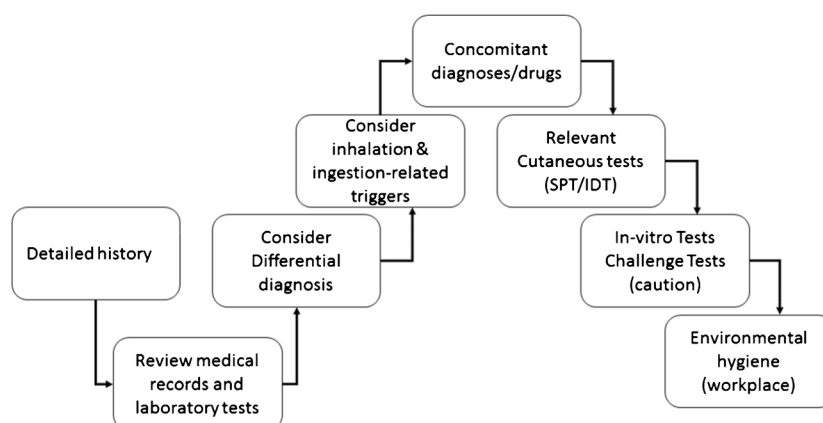


Fig. 2. Steps in the evaluation of occupational anaphylaxis.

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 [86••].

Management of occupational anaphylaxis

At the workplace

Exposure to the trigger should be stopped, either by removal or by allocation of the worker in a different place. Simultaneously, a call for help should be made to a resuscitation team or to emergency medical services. If adrenaline is available, this should be administered while awaiting emergency services [4]. Occupational anaphylaxis often occurs in the absence of a healthcare professional and many people do not know they have an allergy until their first anaphylactic reaction appears and adrenaline may not be available, so it is mandatory to apply emergency measures to maintain the airway and provide cardiopulmonary resuscitation while awaiting emergency services. Any emergency kit (businesses, schools, shopping centers, etc.) shall have medication to treat anaphylaxis, including adrenaline auto-injectors [4, 8, 87].

Emergency management of anaphylaxis

Management of the acute episode is the same as for non-occupational anaphylaxis.

As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with an immediate assessment and maintenance of airway, breathing, circulation, disability, and exposure approach [1, 4, 8]. Deaths result from upper airway, lower respiratory, and/or cardiovascular compromise so emergency management must focus on these manifestations [1].

First-line intervention

Epinephrine (adrenaline) should be administered both to all patients suffering anaphylaxis and to those that are likely to evolve into anaphylaxis [1]. The dose (1 mg/mL) 0.3–0.5 mg in adults should be injected through the intramuscular route into the mid-anterolateral thigh, and the patient should be placed in a recumbent position (or if dyspneic or vomiting, placed in a position of comfort) with the lower extremities elevated to conserve the circulatory volume. When indicated at any time during the episode, additional important steps include administering supplemental oxygen and maintaining the airway, establishing intravenous access, and giving fluid resuscitation. Prompt intramuscular injection of adrenaline, the first-line medication, should not be delayed by taking the time to draw up and administer second-line medications, such as antihistamines and glucocorticoids. These medications are not life-saving because they do not relieve upper airway obstruction (laryngeal edema), hypotension, or shock. Patients with moderate respiratory or cardiovascular compromise should be monitored for at least 4 h and, if indicated, for 8 to 10 h or

longer, and patients with severe or protracted anaphylaxis might require monitoring and interventions for days.

There is no absolute contraindication to epinephrine as treatment of anaphylaxis [88]. However, risk benefit should be weighed in the case of patients with concomitant cardiovascular disease [89]. Nonetheless, the heart is a potential target organ in anaphylaxis. Coronary syndrome can occur during anaphylaxis in the absence of epinephrine [90].

Adrenaline auto-injectors are the preferred method to administer epinephrine in the community setting [79]; Table 3). At the time of discharge from a healthcare setting, an adrenaline auto-injector should be prescribed and patients should be provided with a discharge report that includes the allergen avoidance measures (where possible), and instructions for when and how to use the adrenaline auto-injector. The number of prescribed auto-injectors should be considered. General indications for prescribing two or more devices include high body weight, fear of possible misuse, a history of biphasic or protracted reactions in the past, and concomitant severe asthma [91].

Second-line intervention

Long-term management of anaphylaxis

Removal of the trigger

After a diagnosis of occupational anaphylaxis, the patient should be educated to avoid exposure to the culprit agent, both in and out of the workplace. At the workplace, every measure to prevent further exposure should be carried out, including removal from exposure to the dangerous agent and relocation of the workers. However, if this action is not completely achievable, the risk should be minimized, for example, avoiding the direct manipulation of the culprit allergen or wearing protecting gloves or clothing. In a worker with allergy to Hymenoptera venom and a history of venom-triggered anaphylaxis, immunotherapy for Hymenoptera venom should be considered, as the recent chapter on Hymenoptera venom allergy of the EAACI guidelines on allergen immunotherapy state [92].

These patients should be referred to an allergy specialist for evaluation of their allergy. Venom immunotherapy is a highly effective treatment for

Table 3. Indications for adrenaline auto-injectors adapted from Muraro et al. [1]

Indications for adrenaline auto-injectors

1. Previous (idiopathic) anaphylaxis
2. Exercise-induced anaphylaxis
3. Co-existent unstable or moderate to severe, persistent asthma with food allergy
4. Venom allergy in adults with previous systemic reactions (unless receiving maintenance VIT) and children with more than systemic cutaneous reactions
5. Underlying mast cell disorder and any previous systemic reaction.

individuals with a history of systemic reaction and who have specific IgE to venom allergens and most patients are already protected against bee stings at an early stage of venom immunotherapy [32, 33•].

The recommended starting dose in up-dosing protocols lies between 0.001 and 0.1 µg, but it has also been shown that a starting dose of 1 µg is usually safe and not associated with a higher rate of side effects in adults or in children [92]. A maximum dose of 100 µg venom allergen dose usually offers adequate protection against systemic allergic sting reactions in the majority of venom-allergic individuals [87, 92].

Other immunomodulatory etiological treatments for anaphylaxis include drug desensitization [93], food oral immunotherapy [94], or anti-IgE therapy [95].

Consideration should be given about risk factors that can increase the frequency or severity of a reaction or complicate the treatment. These factors, including exercise, ethanol, NSAIDs, acute infections, stress, and perimenstrual status, potentially amplify anaphylaxis by decreasing the threshold of allergen exposure (the allergen “dose”) needed to trigger anaphylaxis and by amplifying the risk of anaphylaxis in patients with low or borderline allergen [88].

Furthermore, anaphylaxis due to non-occupational allergens, occurring at or exacerbated by the workplace, can be common. Therefore, in any occupational setting where there is a worker with a history of previous anaphylaxis, the accessibility to an emergency written action plan with likely presenting symptoms and how to respond to each as well as the availability of adrenaline and a person trained in its administration is mandatory [3, 88, 96].

Conclusion

Anaphylaxis is a severe and potentially life-threatening systemic allergic response that can be elicited by agents present at the workplace. The most frequent triggers of occupational anaphylaxis are Hymenoptera stings but food, medications, animals, natural rubber latex, and chemicals are also accountable. The mechanisms involved are similar to those of non-occupational anaphylaxis. Cofactors at work, particularly exercise, may increase the risk of developing this clinical emergency. The evaluation of occupational anaphylaxis is very important to confirm the diagnosis and to identify the anaphylaxis trigger. Treatment of the acute episode is the same as for non-occupational anaphylaxis; international guidelines concur that adrenaline is the medication of first choice in anaphylaxis and to those that are likely to evolve into anaphylaxis. Long-term management implies strict avoidance of eliciting agents and removal from exposure. In Hymenoptera-allergic workers, venom immunotherapy treatment, which is highly effective, should be started. A written emergency management plan, health and safety education, and training and surveillance should be enforced in occupations at greater risk.

Compliance with ethical standards

Conflict of interest

Darío Antolín-Amérigo declares that he has no conflicts of interest.

Alberto Álvarez-Perea declares that he has no conflicts of interest.

Ana Fiandor declares that she has no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. •• Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69(8):1026–45.

These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on Anaphylaxis. They aim to provide evidence-based recommendations for the recognition, risk factor assessment, and the management of patients who are at risk of, are experiencing, or have experienced anaphylaxis. While the primary audience is allergists, these guidelines are also relevant to all other healthcare professionals. <https://doi.org/10.1111/all.12437>.

2. •• Simons FE, Arduoso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J*. 2014;7(1):9.

This international consensus is published as an information resource about anaphylaxis for worldwide use by healthcare professionals, academics, policy-makers, patients, caregivers, and the public. <https://doi.org/10.1186/1939-4551-7-9>.

3. Moscato G, Pala G, Crivellaro M, Siracusa A. Anaphylaxis as occupational risk. *Curr Opin Allergy Clin Immunol*. 2014;14(4):328–33. <https://doi.org/10.1097/ACI.0000000000000066>.
4. • Siracusa A, Folletti I, Gerth van Wijk R, Jeebhay MF, Moscato G, Quirce S, et al. Occupational anaphylaxis: an EAACI task force consensus statement. *Allergy*. 2015;70:141–52.

This comprehensive paper delves into the causes of occupational anaphylaxis and also gives practical management strategies for healthcare professionals. <https://doi.org/10.1111/all.12541>

5. Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al. First European data from the network of severe allergic reactions (NORA). *Allergy*. 2014;69(10):1397–404. <https://doi.org/10.1111/all.12475>.

6. de Silva IL, Mehr SS, Tey D, Tang MLK. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy*. 2008;63(8):1071–6. <https://doi.org/10.1111/j.1398-9995.2008.01719.x>.
7. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144–50. <https://doi.org/10.1046/j.1365-2222.2000.00864.x>.
8. Quirce S, Fiandor A. How should occupational anaphylaxis be investigated and managed? *Curr Opin Allergy Clin Immunol*. 2016;16(2):86–92. <https://doi.org/10.1097/ACI.0000000000000241>.
9. Jeebhay MF, Robins TG, Lehrer SB, Lopata AL. Occupational seafood allergy: a review. *Occup Environ Med*. 2001;58(9):553–62. <https://doi.org/10.1136/oem.58.9.553>.
10. Monsalve RI, González de la Peña MA, López-Otín C, Fiandor A, Fernández C, Villalba M, et al. Detection, isolation and complete amino acid sequence of an aeroallergenic protein from rapeseed flour. *Clin Exp Allergy*. 1997;27(7):833–41. <https://doi.org/10.1046/j.1365-2222.1997.660843.x>.
11. Davidson AE, Passero MA, Settignano GA. Buckwheat-induced anaphylaxis: a case report. *Ann Allergy*. 1992;69(5):439–40.
12. García-Abujeta JL, Rodríguez F, Maquieira E, Picans I, Fernández L, Sánchez I, et al. Occupational protein contact dermatitis in a fishmonger. *Contact Dermatitis*. 1997;36(3):163–4. <https://doi.org/10.1111/j.1600-0536.1997.tb00404.x>.
13. Escudero C, Quirce S, Fernández-Nieto M, de Miguel J, Cuesta J, Sastre J. Egg white proteins as inhalant allergens associated with baker's asthma. *Allergy*. 2003;58(7):616–20. <https://doi.org/10.1034/j.1398-9995.2003.00201.x>.
14. Jones M, Skidmore A, Glozier N, Welch J, Hunter AS, Cullinan P. Occupational egg allergy in an embryological research facility. *Occup Med*. 2013;63(5):348–53. <https://doi.org/10.1093/occmed/kqt066>.
15. • Feldweg AM. Food-dependent, exercise-induced anaphylaxis: diagnosis and management in the outpatient setting. *J Allergy Clin Immunol Pract*. 2017;5(2):283–8.

Recently, it was demonstrated that exercise is not essential for the development of symptoms, and that if enough of the culprit food is ingested, often with additional augmentation factors, such as alcohol or acetylsalicylic acid, symptoms can be induced at rest in the challenge setting. Thus, food-dependent, exercise-induced anaphylaxis appears to be more correctly characterized as a food allergy syndrome in which symptoms develop only in the presence of various augmentation factors, with exercise being the primary one. <https://doi.org/10.1016/j.jaip.2016.11.022>.

16. Brockow K, Kneissl D, Valentini L, Zelger O, Grosber M, Kugler C, et al. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol*. 2015;135(4):977–984.e4. <https://doi.org/10.1016/j.jaci.2014.08.024>.
 17. Scherf KA, Brockow K, Biedermann T, Koehler P, Wieser H. Wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2016;46(1):10–20. <https://doi.org/10.1111/cea.12640>.
 18. Fukutomi Y, Taniguchi M, Nakamura H, Akiyama K. Epidemiological link between wheat allergy and exposure to hydrolyzed wheat protein in facial soap. *Allergy*. 2014;69(10):1405–11. <https://doi.org/10.1111/all.12481>.
 19. Chinuki Y, Morita E. Wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat protein in soap. *Allergol Int*. 2012;61(4):529–37. <https://doi.org/10.2332/allergolint.12-RAI-0494>.
 20. Airaksinen L, Pallasaho P, Voutilainen R, Pesonen M. Occupational rhinitis, asthma, and contact urticaria caused by hydrolyzed wheat protein in hairdressers. *Ann Allergy Asthma Immunol*. 2013;111(6):577–9. <https://doi.org/10.1016/j.anai.2013.09.025>.
 21. Khalili B, Bardana EJ, Yunginger JW. Psyllium-associated anaphylaxis and death: a case report and review of the literature. *Ann Allergy Asthma Immunol*. 2003;91(6):579–84. [https://doi.org/10.1016/S1081-1206\(10\)61538-4](https://doi.org/10.1016/S1081-1206(10)61538-4).
 22. Antolín-Amérigo D, Sánchez-González MJ, Barbarroja-Escudero J, Rodríguez-Rodríguez M, Álvarez-Perea A, Alvarez-Mon M. Allergic reaction to polyethylene glycol in a painter. *Occup Med (Lond)*. 2015;65(6):502–4. <https://doi.org/10.1093/occmed/kqv072>.
 - 23.●● Whitaker P. Occupational allergy to pharmaceutical products. *Curr Opin Allergy Clin Immunol*. 2016;16:101–6.
- Interesting review about the diagnosis of occupational allergy to drugs, which can be complicated and has been shown to take up to 5 years from the onset of symptoms. <https://doi.org/10.1097/ACI.0000000000000248>
24. Kim JE, Kim SH, Jin JH, Bahn JW, Jin HJ, Ye YM, et al. A case of piperacilline-induced occupational anaphylaxis: detection of serum IgE to piperacillin-HAS conjugate. *J Korean Med Sci*. 2011;26(5):682–5. <https://doi.org/10.3346/jkms.2011.26.5.682>.
 25. Wittczak T, Dudek W, Walusiak-Skorupa J, Swierczynska-Machura D, Palczynski C. Chlorhexidine: still an underestimated allergic hazard for healthcare professionals. *Occup Med*. 2013;63(4):301–5. <https://doi.org/10.1093/occmed/kqt035>.
 26. Sussman GL, Dorian W. Psyllium anaphylaxis. *Allergy Proc*. 1990;11(5):241–2. <https://doi.org/10.2500/108854190778879828>.
 27. Newman MJ, Goel P. An anesthesiologist with an allergy to multiple neuromuscular blocking drugs: a new occupational hazard. *Anesth Analg*. 2010;110(2):601–2. <https://doi.org/10.1213/ANE.0b013e3181c8a6e0>.
 28. Bandino ML, Tankersley MS. Anaphylaxis in an allergy immunotherapy extract-compounding technician after an extract needle stick. *J Allergy Clin Immunol*. 2012;129(1):250–1. <https://doi.org/10.1016/j.jaci.2011.08.028>.
 29. Toletone A, Voltolini S, Passalacqua G, Dini G, Bignardi D, Minale P. Hymenoptera venom allergy in outdoor workers: occupational exposure, clinical features and effects of allergen immunotherapy. *Hum Vaccin Immunother*. 2017;13(2):477–83. <https://doi.org/10.1080/21645515.2017.1264748>.
 30. Cruz S, Vega A, Fernández S, Marqués L, Baltasar M, Alonso A, et al. Report from the Hymenoptera Committee of the Spanish Society of Allergology and Clinical Immunology: immunotherapy with bumblebee venom. *J Investig Allergol Clin Immunol*. 2012;22:372–92.
 31. Bonifazi F, Jutel M, Bilò BM, Birnbaum J, Muller U, and the EAACI Interest Group on Insect Venom Hypersensitivity. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy*. 2005;60(12):1459–70. <https://doi.org/10.1111/j.1398-9995.2005.00960.x>.
 32. Antolín-Amérigo D, Moreno Aguilar C, Vega A, Alvarez-Mon M. Venom immunotherapy: an updated review. *Curr Allergy Asthma Rep*. 2014;14(7):449. <https://doi.org/10.1007/s11882-014-0449-1>.
 - 33.● Alfaya Arias T, Soriano Gómis V, Soto Mera T, Vega Castro A, Vega Gutiérrez JM, Alonso Llamazares A, et al. Key issues in hymenoptera venom allergy: an update. *J Investig Allergol Clin Immunol*. 2017;27(1):19–31.
- Updated review on important diagnostic and management solutions to hymenoptera venom allergy. <https://doi.org/10.18176/jiaci.0123>.
34. Valls A, Pineda F, Belver MT, Caballero T, López-Serrano MC. Anaphylactic shock caused by tick (*Rhipicephalus sanguineus*). *J Investig Allergol Clin Immunol*. 2007;17:277–85.
 35. Acero S, Blanco R, Bartolomé B. Anaphylaxis due to a tick bite. *Allergy*. 2003;58(8):824–5. <https://doi.org/10.1034/j.1398-9995.2003.00211.x>.
 - 36.● Fischer J, Lupberger E, Hebsaker J, Blumenstock G, Aichinger E, Yazdi AS, et al. Prevalence of type I sensitization to alpha-gal in forest service employees and hunters. *Allergy*. 2017;
- Interesting paper which shows the importance of alpha-gal, a new occupational allergen, cross-reactive with red meat. <https://doi.org/10.1111/all.13156>

37. Vega JM, Moneo I, Armentia A, López-Rico R, Curiel G, Bartolomé B, et al. Anaphylaxis to a pine caterpillar. *Allergy*. 1997;52(12):1244–5. <https://doi.org/10.1111/j.1398-9995.1997.tb02532.x>.
38. Morales-Cabeza C, Prieto-García A, Acero S, Bartolomé-Zavala B, Morgado JM, Matito A, et al. Systemic mastocytosis presenting as occupational IgE-mediated anaphylaxis to pine processionary caterpillar. *Ann Allergy Asthma Immunol*. 2016;117:318–37. <https://doi.org/10.1016/j.anai.2016.07.002>
39. Meseguer J, Sánchez-Guerrero IM, Iraola V, Carnés J, Fernández Caldas E. Occupational allergy to aquarium fish food: red midge larva, freshwater shrimp, and earthworm. A clinical and immunological study. *J Invest Allergol Clin Immunol*. 2013;23:462–70.
40. Rankin TJ, Hill RJ, Overton D. Anaphylactic reaction after a laboratory rat bite. *Am J Emerg Med*. 2007;25:985. <https://doi.org/10.1016/j.ajem.2007.02.025>
41. Kampitak T, Betschel SD. Anaphylaxis in laboratory workers because of rodent handling: two case reports. *J Occup Health*. 2016;58(4):381–3. <https://doi.org/10.1539/joh.16-0053-CS>.
42. Torres JA, Pastor-Vargas C, de las Heras M, Vivanco F, Cuesta J, Sastre J. An odorant-binding protein as a new allergen from Siberian hamster (*Phodopus sungorus*). *Int Arch Allergy Immunol*. 2012;157(1):109–12. <https://doi.org/10.1159/000324956>.
43. Watt AD, McSharry CP. Laboratory animal allergy: anaphylaxis from a needle injury. *Occup Environ Med*. 1996;53(8):573–4. <https://doi.org/10.1136/oem.53.8.573>.
44. Gawlik R, Pitsch T, DuBuske L. Anaphylaxis as a manifestation of horse allergy. *World Allergy Organ J*. 2009;2(8):185–9. <https://doi.org/10.1097/WOX.0b013e3181b2fe51>.
45. Cavkaytar Ö, Soyer Ö, Skerel BE. A rare cause of aeroallergen-induced anaphylaxis: horse allergy. *Turk J Pediatr*. 2014;56(4):437–9.
46. Moghtaderi M, Farjadian S, Abbaszadeh Hasiri M. Animal allergen sensitization in veterinarians and laboratory animal workers. *Occup Med*. 2014;64(7):516–20. <https://doi.org/10.1093/occmed/kqu097>.
47. de Medeiros CR, Barbaro KC, de Siqueira França FO, Zanotti AP, Castro FF. Anaphylactic reaction secondary to Bothrops snakebite. *Allergy*. 2008;63(2):242–3. <https://doi.org/10.1111/j.1398-9995.2007.01535.x>.
48. Prescott RA, Potter PC. Hypersensitivity to airborne spitting cobra snake venom. *Ann Allergy Asthma Immunol*. 2005;94(5):600–3. [https://doi.org/10.1016/S1081-1206\(10\)61140-4](https://doi.org/10.1016/S1081-1206(10)61140-4).
49. Madero MF, Gámez C, Madero MA, Fernández-Nieto M, Sastre J, del Pozo V. Characterization of allergens in four South American snake species. *Int Arch Allergy Immunol*. 2009;150(3):307–10. <https://doi.org/10.1159/000222684>.
50. de Pontes LG, Cavassan NR, Creste CF, Junior AL, Arcuri HA, Ferreira RS, et al. Crotoxin: a novel allergen to occupational anaphylaxis. *Ann Allergy Asthma Immunol*. 2016;116(6):579–81. <https://doi.org/10.1016/j.anai.2016.03.015>.
51. Caballero ML, Quirce S. Identification and practical management of latex allergy in occupational settings. *Expert Rev Clin Immunol*. 2015;11:977–92.
- An up-to-date and comprehensive review of occupational allergy to natural rubber latex. <https://doi.org/10.1586/1744666X.2015.1059754>
52. Miaocong W, James M, Jian L. Current prevalence rate of latex allergy: why it remains a problem? *J Occup Health*. 2016;58:138–44.
53. Salcedo G, Diaz-Perales A, Sanchez-Monge R. The role of plant panallergens in sensitization to natural rubber latex. *Curr Opin Allergy Clin Immunol*. 2001;1(2):177–83. <https://doi.org/10.1097/00130832-200104000-00010>.
54. Raulf-Heimsoth M, Rihs HP, Rozynek P, Cremer R, Gaspar A, Pires G, et al. Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (*Hevea brasiliensis*). *Clin Exp Allergy*. 2007;37(11):1657–67. <https://doi.org/10.1111/j.1365-2222.2007.02833.x>.
55. Spaner D, Dolovich J, Tarlo S, Sussman G, Butto K. Hypersensitivity to natural latex. *J Allergy Clin Immunol*. 1989;83(6):1135–7. [https://doi.org/10.1016/0091-6749\(89\)90457-0](https://doi.org/10.1016/0091-6749(89)90457-0).
56. Sussman GL, Tarlo S, Dolovich J. The spectrum of IgE-mediated responses to latex. *JAMA*. 1991;265(21):2844–7. <https://doi.org/10.1001/jama.1991.03460210090035>.
57. de Groot H, Patiwaal JA, de Jong N, Burdorf A, van Wijk RG. Research into sensitization and allergies to latex: results after 10 years of the use of powder-free latex gloves. *Ned Tijdschr Geneesk*. 2013;157:A5835.
58. Helaskoski E, Suojalehto H, Virtanen H, Airaksinen L, Kuuliala O, Aalto-Korte K, et al. Occupational asthma, rhinitis, and contact urticaria caused by oxidative hair dyes in hairdressers. *Ann Allergy Asthma Immunol*. 2014;112(1):46–52. <https://doi.org/10.1016/j.anai.2013.10.002>.
59. Fukunaga T, Kawagoe R, Hozumi H, Kanzaki T. Contact anaphylaxis due to paraphenylenediamine. *Contact Dermatitis*. 1996;35(3):185–6. <https://doi.org/10.1111/j.1600-0536.1996.tb02348.x>.
60. Oshima H, Tamaki T, Oh-I T, Koga M. Contact anaphylaxis due to para-aminophenol and para-methylaminophenol in hair dye. *Contact Dermatitis*. 2001;45(6):359. <https://doi.org/10.1034/j.1600-0536.2001.450610.x>.
61. Kleniewska A, Wiszniewska M, Krawczyk-Szulc P, Nowakowska-Świrta E, Walusiak-Skorupa J. Anaphylactic reaction in a hairdresser due to sensitization to persulphates. *Occup Med (Lond)*. 2016;66(7):584–5. <https://doi.org/10.1093/occmed/kqw037>.
62. Romano C, Sulotto F, Pavan I, Chiesa A, Scansetti G. A new case of occupational asthma from reactive dyes with severe anaphylactic response to the specific

- challenge. *Am J Ind Med*. 1992;21(2):209–16. <https://doi.org/10.1002/ajim.4700210210>.
63. Nowak D, Panaszek B. Anaphylactic reactions to low-molecular weight chemicals. *Postepy Hig Med Dosw (Online)*. 2015;69:197–206.
 64. Krecisz B, Kiec-Swierczynska M, Krawczyk P, Chomiczewska D, Palczynski C. Cobalt-induced anaphylaxis, contact urticaria, and delayed allergy in a ceramics decorator. *Contact Dermatitis*. 2009;60(3):173–4. <https://doi.org/10.1111/j.1600-0536.2008.01465.x>.
 65. Littorin M, Truedsson L, Welinder H, Skarping G, Martensson U, Sjöholm AG. Acute respiratory disorder, rhinoconjunctivitis and fever associated with the pyrolysis of polyurethane derived from diphenylmethane diisocyanate. *Scand J Work Environ Health*. 1994;20(3):216–22. <https://doi.org/10.5271/sjweh.1405>.
 66. Scolnick B, Collins J. Systemic reaction to methylmethacrylate in an operating room nurse. *J Occup Med*. 1986;28(3):196–8.
 67. Li LF, Sujan SA, Li QX. Contact urticaria syndrome from occupational benzonitrile exposure. *Contact Dermatitis*. 2004;50(6):377–8. <https://doi.org/10.1111/j.0105-1873.2004.0350e.x>.
 68. Lessenger JE. Occupational acute anaphylactic reaction to assault by perfume spray in the face. *J Am Board Fam Pract*. 2001;14(2):137–40.
 69. Hannu T, Alanko K, Keskinen H. Anaphylaxis and allergic contact urticaria from occupational airborne exposure to HBTU. *Occup Med (Lond)*. 2006;56(6):430–3. <https://doi.org/10.1093/occmed/kql025>.
 70. Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol*. 2012;157(3):275–80. <https://doi.org/10.1159/000329856>.
 - 71.●● Álvarez-Perea A, Tomás-Pérez M, Martínez-Lezcano P, Marco G, Pérez D, Zubeldia JM, et al. Anaphylaxis in adolescent/adult patients treated in the emergency department: differences between initial impressions and the definitive diagnosis. *J Investig Allergol Clin Immunol*. 2015;25:288–94.
- This paper highlights the importance of a correct diagnosis of anaphylaxis, which conditions the administration of epinephrine, regardless of the severity of symptoms. The real etiology of anaphylaxis should only be proposed after an allergy workup, which is recommended in all cases, as the real cause can differ considerably from the initial impression in the ED.
72. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Estes O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. *Int Arch Allergy Immunol*. 2013;160(2):192–9. <https://doi.org/10.1159/000339749>.
 73. Cardona V, Álvarez-Perea A, Ansotegui IJ, Arias-Cruz A, González-Díaz SN, Latour-Staffeld P, et al. Management of anaphylaxis in Latin America: current situation. *Rev Alerg Mex*. 2017;64(2):171–7.
 74. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391–7. <https://doi.org/10.1016/j.jaci.2005.12.1303>.
 75. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, et al. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol*. 2012;129(3):748–52. <https://doi.org/10.1016/j.jaci.2011.09.030>.
 76. Loprinzi Brauer CE, Motosue MS, Li JT, Hagan JB, Bellolio MF, Lee S, et al. Prospective validation of the NIAID/FAAN criteria for emergency department diagnosis of anaphylaxis. *J Allergy Clin Immunol Pract*. 2016;4(6):1220–6. <https://doi.org/10.1016/j.jaip.2016.06.003>.
 77. Campbell RL, Park MA, Kueber MA, Lee S, Hagan JB. Outcomes of allergy/immunology follow-up after an emergency department evaluation for anaphylaxis. *J Allergy Clin Immunol Pract*. 2015;3(1):88–93. <https://doi.org/10.1016/j.jaip.2014.07.011>.
 78. Álvarez-Perea A, Ameiro B, Morales C, Zambrano G, Rodríguez A, Guzmán M, et al. Anaphylaxis in the pediatric emergency department: analysis of 133 cases after an allergy workup. *J Allergy Clin Immunol Pract*. 2017;5(5):1256–63. <https://doi.org/10.1016/j.jaip.2017.02.011>.
 79. Simons FE, Arduoso LR, Bilò MB, El-Gamal YM, Ledford MD, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol*. 2011;127(3):587–93. <https://doi.org/10.1016/j.jaci.2011.01.038>.
 80. Quirce S. IgE antibodies in occupational asthma: are they causative or an associated phenomenon? *Curr Opin Allergy Clin Immunol*. 2014;14(2):100–5. <https://doi.org/10.1097/ACI.0000000000000041>.
 81. Caballero ML, Ordaz E, Bermejo M, Rodríguez-Pérez R, Alday E, Maqueda J, et al. Characterization of occupational sensitization by multiallergen immunoblotting in workers exposed to laboratory animals. *Ann Allergy Asthma Immunol*. 2012;108(3):178–81. <https://doi.org/10.1016/j.anai.2012.01.007>.
 82. Cardona V, Ansotegui IJ. Component-resolved diagnosis in anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2016;16:244–9.
 83. Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD, et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin*

- Immunol. 2007;120(1 Suppl):S2–24. <https://doi.org/10.1016/j.jaci.2007.05.001>.
84. Hompes S, Kohli A, Nemat K, Scherer K, Lange L, Rueff F, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents—data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol.* 2011;22(6):568–74. <https://doi.org/10.1111/j.1399-3038.2011.01154.x>.
 85. Tewari A, TG D, Lack G. The difficulties of diagnosing food-dependent exercise-induced anaphylaxis in childhood—a case study and review. *Pediatr Allergy Immunol.* 2006;17(2):157–60. <https://doi.org/10.1111/j.1399-3038.2005.00374.x>.
 - 86.●● Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update. *Ann Allergy Asthma Immunol.* 2015;115:341–84.
- An extensive review and recommendations about anaphylaxis and its management written by the American Academy of Allergy, Asthma and Immunology (AAAAI).
87. Bilò MB, Cichocka-Jarosz E, Pumphrey R, Oude-Elberink JN, Lange J, Jakob T, et al. Self-medication of anaphylactic reactions due to Hymenoptera stings—an EAACI Task Force Consensus Statement. *Allergy.* 2016;71(7):931–43. <https://doi.org/10.1111/all.12908>.
 88. Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization Anaphylaxis Guidelines. *World Allergy Organ J.* 2015;8:32.
 89. Lieberman P, Simons FER. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. *Clin Exp Allergy.* 2015;45(8):1288–95. <https://doi.org/10.1111/cea.12520>.
 90. Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol.* 2008;153(Suppl 1):7–11. <https://doi.org/10.1111/j.1365-2249.2008.03714.x>.
 91. Niggemann B, Beyer K. Adrenaline autoinjectors in food allergy: in for a cent, in for a euro? *Pediatr Allergy Immunol.* 2012;23(6):506–8. <https://doi.org/10.1111/j.1399-3038.2012.01300.x>.
 - 92.● Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy.* 2017.
- Comprehensive up-to-date systematic review about the evidence on venom immunotherapy of the European Academy of Allergy and Clinical Immunology.
93. Castells MCA. New era for drug desensitizations. *J Allergy Clin Immunol Pract.* 2015;3(4):639–40. <https://doi.org/10.1016/j.jaip.2015.05.006>.
 94. Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy.* 2017;72(8):1133–47. <https://doi.org/10.1111/all.13124>.
 95. El-Qutob D. Off-label uses of omalizumab. *Clin Rev Allergy Immunol.* 2016;50(1):84–96. <https://doi.org/10.1007/s12016-015-8490-y>.
 96. Simons FE, Arduzzo LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, et al. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol.* 2013;162(3):193–204. <https://doi.org/10.1159/000354543>.