

# Prevention of Anaphylaxis Based on Risk Factors and Cofactors

Bernard Yu-Hor Thong, MBBS, MRCP (UK), FRCP (Edin)

## Address

Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital,  
11 Jalan Tan Tock Seng, Singapore, 308433, Singapore  
Email: [bernard\\_thong@ttsh.com.sg](mailto:bernard_thong@ttsh.com.sg)

Published online: 13 July 2016

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This article is part of the Topical Collection on *Anaphylaxis*

**Keywords** Drug hypersensitivity · Food hypersensitivity · Hymenoptera · Immunotherapy · Quality of life

## Opinion statement

Anaphylaxis is most commonly caused by drugs, food, and hymenoptera stings, or in certain instances may be idiopathic. A variety of risk factors, cofactors, and augmenting factors may act together to trigger anaphylaxis. Patients with certain underlying medical conditions may be at increased risk of anaphylaxis of certain etiologies, e.g., monoclonal mast cell activation syndromes and insect venom anaphylaxis, asthma, and fatal food-induced anaphylaxis especially in adolescents. Identification of risk factors, cofactors, and augmenting factors during clinical assessment is key to determining the type of in vitro and in vivo diagnostic tests that would be most appropriate in accurately identifying the putative allergen(s). Provocation tests, despite being the gold standard in allergy diagnosis, should be avoided in anaphylaxis as the risks outweigh the benefits. Accurate diagnosis of the putative allergen and cofactor is key to both prevention of recurrence of anaphylaxis, avoidance measures, and interventions like allergen-specific immunotherapy, which may impact the quality of life of allergy sufferers and their family members.

## Introduction

Anaphylaxis is a serious, life-threatening generalized or systemic hypersensitivity reaction that may be potentially fatal [1] [2••] [3]. Although common causes of anaphylaxis include foods, drugs, insect venom stings, natural rubber latex, allergen-specific immunotherapy, and physical factors, there are age group [4], regional, and ethnic differences [5]. For instance, food-induced anaphylaxis is more common in children [6, 7] whereas hymenoptera

sting [8, 9] and drug-induced anaphylaxis [10, 11] are more common among adults.

Recent guidelines [1] [2••] on the diagnosis and management of anaphylaxis have identified important risk factors and cofactors that trigger or augment anaphylaxis. Risk factors have been further classified into augmenting factors, concomitant diseases, and cofactors by some authors [2••] [12]. Augmenting factors are defined as factors which

lower the reaction threshold or increase the severity of allergic symptoms. They do so by directly influencing the immunological mechanism of type I hypersensitivity (allergic) reactions, e.g., physical exercise, acute infections, certain drugs like non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, and menstruation. Concomitant diseases like asthma, mastocytosis, or cardiovascular disease increase the risk of mortality in anaphylaxis. Cofactors are defined as risk factors which do not directly influence the allergen-immunoglobulin E (IgE)-effector cell interactions. These include certain allergens like peanuts, certain developmental stages like adolescence, psychological factors like emotional stress, or drugs like angiotensin-converting enzyme (ACE) inhibitors. Some other authors use

the term “cofactors” interchangeably with augmenting factors [13].

We review the different risk factors and cofactors in anaphylaxis and their role(s), if any, in the following:

- Primary prevention in those who have never had anaphylaxis (e.g., breastfeeding and hypoallergenic formulas for infants at risk of food allergy) [14]
- Secondary prevention in individuals who have developed anaphylaxis (e.g., food labeling laws for prevention of food allergy [15•], allergen immunotherapy for prevention of allergic diseases [16] [17••], desensitization in anaphylaxis to aspirin [18], chemotherapeutic agents and biologics in patients with cancer and rheumatological disorders [19])

## Prevention and treatment

A careful analysis of risk factors, cofactors, and augmenting factors needs to be undertaken from careful clinical history and physical examination. This is followed by utilization of appropriate in vitro and/or in vivo tests to identify the causative allergen(s) before definitive treatment and preventive measures can be instituted.

### Risk factors

Identification of risk factors for anaphylaxis is important in overall management of anaphylaxis because risk stratification may increase the clinical suspicion for diagnosis and affect the individual's self-management abilities. These include the following:

- Age—infants, adolescence, elderly
- Pregnancy—during labor and delivery
- Past history of severe allergic reactions (food)
- Occupational exposures
- Special populations: spina bifida and healthcare workers (natural rubber latex anaphylaxis), recurrent infections (infectious diseases), oncology patients (anaphylaxis to chemotherapeutic agents and monoclonal antibodies)

### Age

In children, food is the most common cause of anaphylaxis especially during the weaning period when cow's milk, egg, and peanut are common allergens. The diagnosis of anaphylaxis in infants can be particularly difficult as they may present with features indistinguishable from that of healthy infants, e.g., irritability, inconsolable crying,

flushing, dysphonia, and drooling. Objective measures like blood pressure, heart rate, and respiratory rate also need to be interpreted using age-dependent reference intervals [20•]. The infant/child with established anaphylaxis depends on the caregiver, family, school to participate in allergen avoidance measures, and epinephrine autoinjector (EAI) use until the child is of school-going age [21]. The absence of EAI for infants and very young children well below 15 kg body weight may necessitate the use of epinephrine syringes which are a challenge even for adult caregivers to draw up during emergencies. Natural desensitization in childhood cow's milk and egg allergy can occur in up to 85 % of children with dietary elimination over time, which is distinct from adult onset food allergies which is usually permanent.

Adolescence is a high risk period for anaphylaxis because of risk-taking behavior, poor judgment of actions during reactions, and non-adherence [22]. A tripartite management framework integrating better understanding of the developmental period of adolescence; incorporation of the constituents of adolescents' social networks (including impact of social media); and adolescent-tailored healthcare perspectives has been proposed for the transition of care of adolescents with anaphylaxis to adult services [23].

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## Elderly

Anaphylaxis from drugs and insect venom stings has been associated with the highest rates of fatality among the elderly [24], where drugs are the most common cause [25]. Polypharmacy is an important risk factor in this age group. Important causative drugs include NSAIDs, beta-blockers, and ACE inhibitors (for heart failure) which may act as both the trigger or cofactor to augment an anaphylactic reaction. NSAIDs may cause anaphylaxis via both IgE-mediated (single NSAID reactors) or more commonly non-IgE-mediated mechanisms (cross-reactors from cyclooxygenase inhibition), whereas ACE-inhibitor non-allergic drug hypersensitivity is bradykinin-mediated. Anaphylaxis can be potentially prevented in these individuals by using alternative drugs. Drugs for which there is a clinical need can still be prophylactically desensitized should there be no other suitable alternative [26•], e.g., elderly patients with anaphylaxis from aspirin who now have cardiovascular disease [18], or patients with cancer who have developed recent anaphylaxis during the use of chemotherapy and biologic agents [19].

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## Pregnancy

During pregnancy, anaphylaxis can have catastrophic outcomes on both the mother and fetus if not managed properly [27•]. Symptoms and signs of anaphylaxis intrapartum may be atypical. These can include intense pruritis affecting the vulva and vagina, low back pain, uterine cramps, preterm labor, and fetal distress. During the first three trimesters, the causes of anaphylaxis are similar to those in non-pregnant women. During labor and delivery,  $\beta$ -lactam antibiotics,

natural rubber latex [28], and other agents used in medical and peri-operative settings [29] are common causes of anaphylaxis. Parenteral iron has also been recently implicated in cases of intrapartum [30] and postpartum anaphylaxis [31]. Other than the usual emergency management of anaphylaxis in a non-pregnant female, management in the pregnant female includes positioning the mother left lateral to improve venous return to the heart, maintaining a minimum maternal systolic blood pressure of 90 mmHg to ensure adequate placental perfusion, and continuous electronic monitoring.

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### Past history of severe allergic reactions

A history of severe allergic events including anaphylaxis is a risk factor for future food-induced anaphylaxis [32••] [33] [34]. During oral immunotherapy for cow's milk, not having to use injectable epinephrine during induction was a predictor of achieving the full dose of cow's milk protein [35, 36]. High basophil allergen CD63 sensitivity phenotype was a major indicator of severe adverse systemic reactions during the buildup (induction) phase of honeybee venom immunotherapy [37].

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### Occupational exposures

Occupational anaphylaxis may occur in certain at-risk occupations [38••]. Examples include food processors (food proteins like wheat, spices), beekeepers (hymenoptera stings), healthcare workers (natural rubber latex, drugs), and individuals who work with animals (animal bites) [39]. Primary prevention comprises reducing/avoiding exposure to the causative or sensitizing agents and mitigating host-related factors (poorly controlled asthma, cardiovascular disease) among workers exposed to agents at high risk of causing anaphylaxis in the workplace. It also comprises substitution with a safer product at work (e.g., latex-free gloves), reduction of exposure (e.g., psyllium granules in place of powder), containment (e.g., use of robotics), use of personal protective equipment, and improved workplace ventilation. Secondary preventive measures comprise focused medical surveillance of high-risk working populations (e.g., with questionnaires or immunological testing), health and safety education, and training of workers to read product labels in order to recognize potential allergens. Tertiary prevention comprises early recognition and diagnosis of an anaphylactic reaction, followed by appropriate removal from further exposure [39]. Other than avoidance and being self-equipped with an EAI, allergen-specific immunotherapy is also recommended in workers with hymenoptera sting anaphylaxis [40].

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### Other special populations

Although certain patient populations like those with spina bifida/myelomeningoceles and recurrent surgeries are at risk for natural

rubber latex sensitization and hence anaphylaxis [41], the risk can now be mitigated through prevention with the use of latex-free gloves and a latex-free environment when managing at-risk patients [42, 43]. Allergen-specific immunotherapy has not been shown to be effective in natural rubber latex anaphylaxis [43].

### Concomitant diseases

Concomitant diseases which increase the risk of severe anaphylaxis include the following:

- Asthma and allergic disease load (in food-induced anaphylaxis)
- Mastocytosis/monoclonal mast cell disorders (in hymenoptera, NSAID, and drug-induced anaphylaxis with certain drugs)

### Asthma and allergic disease load

Asthma is a major risk factor for fatal food-induced anaphylaxis, with case series describing 69–100 % of patients having preexisting asthma [32••]. During oral immunotherapy with cow's milk, patients with asthma are at risk for more severe reactions and less likely to achieve full desensitization [36].

### Mastocytosis/monoclonal mast cell disorders

Mast cell activation syndrome (MCAS) can be diagnosed in patients with severe, recurrent symptoms as a consequence of the release of mast cell (MC)-derived mediators [44••]. When KIT-mutated, clonal MC are detected in such patients, primary MCAS can be diagnosed. Patients with primary MCAS and hymenoptera anaphylaxis [45] are predominantly males, often lack skin lesions, and develop anaphylaxis characterized by hypotension and syncope in the absence of urticaria and angioedema. Lifelong venom immunotherapy protects these individuals from further potentially fatal severe reactions. They may also develop anaphylaxis to certain drugs in particular general anesthetic agents [46•] and less commonly NSAIDs [47].

### Cofactors

Cofactors or augmentation factors reduce the threshold for anaphylaxis. The importance of identifying these is that in the absence of the cofactor, anaphylaxis may not occur. This becomes important in the diagnosis (e.g., negative provocation tests) and prevention of future anaphylactic episodes (e.g., management of individuals with wheat-dependent exercise-induced anaphylaxis, WDEIA).

### Physical exercise

Exercise can induce anaphylaxis through mechanisms which remain unknown [48, 49]. This may be food-dependent or non-food dependent and involves exercising up to a certain threshold, in particular within 4 h of ingestion of the food allergen. The most well-characterized food allergen that may cause food-dependent exercise-induced anaphylaxis (FDEIA) is

wheat. WDEIA often occurs in teenagers and younger individuals. The diagnosis is based on a high index of clinical suspicion supported by an accurate history of anaphylaxis within 4 h of wheat ingestion. Skin prick tests (SPTs) and specific IgE to wheat, gluten, and omega-5 gliadin should be performed. An oral food challenge followed by a maximal exercise on a treadmill may not confirm the diagnosis. This is because several cofactors may be missed in a controlled challenge environment, for instance, the intensity of exercise, environmental pollen exposure, concomitant ingestion of non-steroidal anti-inflammatory drugs or alcohol, and the presence of menses in females [50] [51••]. The presence of IL-4-C590T polymorphism may also influence the onset of WDEIA [52].

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### Acute infection

Acute infections may act as a cofactor and increase the risk of anaphylaxis. This has been reported in 1.3–11 % in adults [53, 54] and 2.5–3 % of anaphylactic reactions in children [54, 55] from anaphylaxis registries. Failure to postpone injection allergen immunotherapy following an acute infection is also associated with a risk of anaphylaxis [56]. The absence of infection as a cofactor may also result in falsely negative drug provocation tests [57, 58] especially in the setting of NSAID hypersensitivity reactions [59]. Hence, negative drug provocation tests confirmed by tolerance to a course of NSAID [60] or betalactam antibiotic [61] during a subsequent real-world infective episode would be the best proof of tolerance.

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### Menstrual status

Although there is a female predisposition to developing atopy and IgE-mediated allergic diseases [62], registry studies have not consistently shown any gender differences for anaphylaxis, although some series have shown insect venom anaphylaxis to be more common in males because of differences in exposure to hymenoptera [63].

Anaphylaxis related to menstrual cycles is also known as catamenial anaphylaxis [64]. There is inconsistent evidence as to whether the mechanism that causes this cyclical anaphylaxis [65] involves hypersensitivity to progesterone or prostaglandins. WDEIA episodes exacerbating catamenial anaphylaxis have also been reported [66]. Management [67] involving cessation of the menstrual cycle by means of induction of medical (e.g., leuprolide, a luteinizing hormone releasing hormone agonist [68]) or surgical menopause (total hysterectomy and bilateral salpingo-oophorectomy) results in control of most such anaphylactic reactions. Progestogen desensitization has recently been described in particular in preserving fertility in patients undergoing in vitro fertilization [69].

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### Emotional stress

Anaphylaxis registries have described emotional stress as a cofactor for anaphylaxis. However, there remains paucity of published evidence

that emotional stress is an important cofactor for anaphylaxis [70]. Food-allergic young adults with previous episodes of anaphylaxis appear to be at risk for psychological distress for fear of developing a recurrence of anaphylaxis rather than having stress trigger anaphylaxis per se [71]. In undifferentiated somatoform idiopathic anaphylaxis [72], patients may present with non-specific symptoms (e.g., dizziness, pruritus, flushing, shortness of breath) suggestive of anaphylaxis but with few objective clinical signs during the acute attack to support a diagnosis of anaphylaxis. These psychosomatic symptoms have to be differentiated from genuine anaphylaxis, especially during subsequent episodes.

## Alcohol

Although alcohol has been implicated as a potential cofactor in anaphylaxis reactions; the pathomechanisms remain unclear, and there remains paucity of literature on this entity [73].

## In vivo and in vitro diagnostic tests

In vivo tests, specifically skin tests, are widely used and have been validated in the identification of the putative allergen in IgE-mediated drug [74], food [75], occupational [76], and hymenoptera sting anaphylaxis. Drug concentrations for skin prick and intradermal tests have been established for a variety of drugs as overly concentrated drugs may cause irritative reactions on skin testing, e.g., beta-lactam antibiotics and neuromuscular blocking agents [77•]. For foods, mean skin test wheal size [78] has been found to correlate with positive outcomes of double-blind placebo-controlled food challenges for certain foods, e.g., cow's milk and egg. For fresh fruit and vegetables, prick-to-prick tests are more sensitive than commercial extracts [79, 80]. Specific cutoff levels for food-specific IgE for certain foods like cow's milk, egg, and peanut have been determined and found to be predictive of both positive and negative double-blind placebo-controlled food challenges [81, 82]. For natural rubber latex allergy, performance characteristics for different latex-specific IgE assays vary due to different methodologies of the test assay, composition of latex allergens in the assay, and whether the comparator was the index reaction or a result of the latex glove test [83, 84].

Molecular allergy diagnosis using component resolved diagnostic (CRD) [85] tests where recombinant or purified single allergens are used to detect serum-specific IgE is becoming increasingly important in the diagnosis of certain types of anaphylactic reactions involving cofactors, e.g., WDEIA, where IgE specific for omega-5-gliadin in wheat extract has high positive predictive value for WDEIA [51•]. CRD may also be able to differentiate the different phenotypes of egg-allergic individuals, e.g., those who tolerate extensively heated egg and those in whom egg allergy resolves over time [86]. CRD is also important in differentiating allergens with high potential for

anaphylaxis (e.g., prolamin, seed storage proteins in plant allergens) from cross-reactive carbohydrate determinants in food [87•]. In insect venom anaphylaxis, CRD has the potential to improve diagnosis in particular in individuals who are equivocal or test negative using traditional specific IgE assays and skin tests or those who test positive for two venoms [88]. Basophil activation tests using flow cytometry-assisted analysis and quantification of in vitro activated basophils have been extensively investigated in food, insect venom, and drug allergy [89] [90•]. To date, the most useful application has been shown to be in the diagnosis of immediate drug hypersensitivity, with the most data from neuromuscular blocking agents and beta-lactam antibiotics [91]. However, the utility of the basophil activation test is limited by difficulties with preparation of activated basophils, characterization and validation of allergen extracts, and the availability of more easily accessible commercial test assays.

Provocation tests remain the gold standard for confirmation of food and drug allergy [92]. However, they are often impractical or unethical to carry out if the index reaction was anaphylaxis, where the risk of recurrence far outweighs the benefits. Where in vivo and in vitro tests are negative, it may be still be impractical to carry out provocation tests in certain instances to demonstrate clinical tolerance, e.g., neuromuscular blocker or radiocontrast media drug provocation tests, and sting challenges. In food allergy, threshold-eliciting doses for using low-dose, double-blind, placebo-controlled food challenges have been determined for certain food allergens like peanut, hazelnut, celery, fish, and shrimp [93]. The eliciting dose for peanut has also been shown to be significantly and inversely correlated with peanut- and Ara h 2-specific IgE levels, skin prick test responses, basophil activation, and TH2 cytokine production by peripheral blood mononuclear cells [94]. In food challenges, adding cofactors like additives and exercise may modify the outcomes of these challenges [95, 96].

## Conclusions

In any patient with anaphylaxis, a careful assessment of the risk factors, cofactors, and augmenting factors needs to be made as these will affect the diagnostic evaluation and hence management, especially when instituting secondary or primary prevention. Although various in vitro and in vivo tools are available, the performance of these tools including sensitivity, specificity, and predictive values vary depending on the study design, allergen in question, and whether the comparator is the index reaction or a result of provocation tests. A combination of both in vitro and in vivo techniques in selected patients may be useful in increasing the diagnostic accuracy of these tests, thus further reducing the need for provocation tests. Accurate diagnosis of the putative allergen and cofactor is key to prevention of recurrence of anaphylaxis. Avoidance measures (prevention) and therapeutic interventions like allergen-specific immunotherapy may impact on the quality of life of

both the individual and family members with food [97, 98], drug [99], and hymenoptera [100] anaphylaxis.

## Compliance with Ethical Standards

### Conflict of Interest

Bernard Yu-Hor Thong declares that he has no conflict 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.

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