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Anaphylaxis (M Sánchez-Borges, Section Editor)

Risk Factors and Cofactors for Severe Anaphylaxis

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Abstract

Purpose of review Severe anaphylaxis is a generalized reaction in which cardiovascular and respiratory involvement lead to a fatal or near-fatal outcome. Triggers of severe anaphylaxis differ from one age group to another and are mostly represented by drugs and hymenoptera stings in adults and food in children. Several risk factors and cofactors can increase the odds of severe anaphylaxis by different and still undefined mechanisms.
Recent findings Major risk factors for severe anaphylaxis include old age, male sex, and preexisting medical conditions such as mast cell disorders, cardiovascular diseases, and uncontrolled asthma. Antihypertensive drugs appear to increase the severity of anaphylaxis probably by impairing compensatory mechanism to support blood pressure during the reaction. Severe reactions are also associated with transient cofactors such as exercise following specific allergen exposure, treatment with nonsteroidal anti-inflammatory drugs, and alcohol consumption.
Summary Identification of risk factors and potential concurrent cofactors for each individual patient is mandatory to prevent severe anaphylaxis. Risk stratification is crucial to develop personalized prevention strategies and action plans to avoid potentially life-threatening reactions.

Introduction

Anaphylaxis is a potentially life-threatening, generalized reaction, characterized by a rapid onset of cutaneous, respiratory, gastrointestinal, and cardiovascular symptoms that can lead to death. Definition of severe anaphylaxis is still difficult due to different classifications and grading of the reaction [1, 2]. Clinically, we refer to severe anaphylaxis in cases of a fatal or near-fatal event requiring hospitalization and life-supporting measures. The prevalence of anaphylaxis, diagnosed according to the WAO/EAACI guidelines [3, 4••], has been rising over recent decades with an estimated lifetime prevalence of 0.5–2% in the general population [4••, 5, 6]. Despite the increasing prevalence, fatality rates have remained stable over the last decades [3, 6, 7].

While anaphylaxis may be severe since its first presentation in a patient, fatal cases often occur after previous milder episodes have been experienced. In addition, certain patients may develop a severe reaction under circumstances that had previously induced a mild or no reaction. This observation supports the concept that initiation of anaphylaxis and severity of the reaction are not only related to the type of trigger but also to temporary or permanent factors related to the patient. Examples of these factors are patients with certain diseases, such as mast cell disorders or cardiovascular diseases, which appear to be at higher risk of severe reactions [8, 9••].

Risk factors and cofactors of severe anaphylaxis

Anaphylaxis is a heterogeneous condition because of a pleomorphic clinical presentation and of different patient outcomes. Both depend on either the triggers of the reaction or patient's conditions. The latter can be temporarily or persistently influenced by several factors which can be differentiated in risk factors and cofactors.

In this review, we will consider *risk factors* as any preexisting condition or event that can increase the chance of inducing anaphylaxis. By contrast, a *cofactor* will be considered as any temporary or persistent factor or condition that can increase the severity of anaphylaxis, such as concomitant use of drugs, allergen type, and amount and route of administration [10]. However, the definition of risk factors and cofactors is quite arbitrary, since there is not always a clear differentiation between them and risk factors and cofactors frequently overlap.

Risk factors of severe anaphylaxis

Several epidemiological studies confirmed that *age* is one of the most important determinants of anaphylaxis severity. A recent study from the European Registry of Anaphylaxis showed that each increasing year was associated with a 1.6% increase in the odds of developing severe anaphylaxis [9••]. The higher risk of severe reactions in the elderly has been attributed not only to a higher drug use in this group (see the "Cofactors in severe anaphylaxis" section) but also to concomitance of cerebrovascular or cardiovascular diseases that reduce patient's ability to activate compensatory mechanisms to counteract the main features of anaphylaxis (hypotension, hypoxia, arrhythmias) [11, 12].

Cardiovascular dysfunction can be considered a primary cause of death in patients with anaphylaxis. A preexisting ischemic heart disease, particularly if

associated with dilated cardiomyopathy, is a negative prognostic factor for severe anaphylaxis [13, 14]. Mast cells are physiologically present in the normal heart mostly located within the adventitia of large coronary vessels and around small intramural coronary arteries. The number of cardiac mast cells is greatly increased in patients with ischemic heart disease and dilated cardiomyopathy [15]. The strategic location of cardiac mast cells around coronary arteries may explain why coronary blood flow and myocardial function are frequently altered in anaphylaxis. While histamine induces a decrease in the mean aortic pressure and an increase in coronary flow in healthy individuals, this mediator decreases coronary flow and may induce coronary spasm in patients with cardiovascular diseases and coronary atherosclerosis [16]. Other mast cell mediators, including cysteinyl leukotrienes (CysLTs) and platelet-activating factor (PAF), have an important role in worsening cardiovascular involvement in anaphylaxis. CysLTs are potent coronary constricting agents, act on Purkinje cells and can cause arrhythmias. PAF can induce a severe reduction of coronary blood flow; it greatly reduces myocardial contractility and may promote arrhythmias by interacting with ionic channels on myocardiocytes. Finally, PAF induces platelet aggregation and amplifies the coagulation cascade potentially causing thrombosis in the course of anaphylaxis [17, 18].

Recent data indicate that *male sex* is associated with severe anaphylaxis with an odd ratio between 1.16 and 1.92 depending on the grading system used for definition of anaphylaxis severity [9••]. Other studies failed to confirm these findings [3], probably because the predominant triggers of the reaction, e.g., hymenoptera sting vs. food, may influence differentially the statistical analysis. Therefore, the real impact of sex as a risk factor remains to be established.

Mast cell disorders are a heterogeneous group of diseases characterized by an abnormal expansion and/or activation of mast cells. These disorders include mastocytosis and mast cell activation syndromes (MCAS), either monoclonal or non-clonal. MCAS is diagnosed when all the following three criteria are met: (a) recurrent systemic (usually severe) symptoms of mast cell activation, including anaphylaxis, (b) evidence of mast cell activation during the acute episodes, such as an increase in serum tryptase level (at least 20% of baseline level plus 2 ng/mL) during (or shortly after) an event, and (c) complete response of symptoms to anti-mediator-type treatment. The prevalence of anaphylaxis has been reported to be significantly higher in patients with mastocytosis as compared to the general population with an overall frequency ranging from 22 to 49%. Prevalence is higher in those without skin lesions of *urticaria pigmentosa* [19–21]. Furthermore, 10–20% of patients with mastocytosis may experience at least one episode of severe anaphylaxis [22]. Hymenoptera stings represent the most common trigger of anaphylaxis in these patients [19].

Several studies have shown that the rate of mast cell proliferation is inversely related with the severity of mediator-related symptoms; in fact, anaphylaxis is more frequent in patients with indolent than in those with advanced mastocytosis [19]. Baseline tryptase levels can be used to predict patients with mastocytosis at risk for venom-induced severe anaphylaxis [23, 24].

Patients without skin lesions are at higher risk of anaphylaxis probably because mastocytosis in these patients is not easily diagnosed and is undertreated. However, several groups of investigators proposed that the

absence of skin lesions identifies a specific phenotype of mastocytosis in which the anaphylaxis-eliciting factor is almost exclusively limited to hymenoptera sting. Besides the lack of skin involvement, this phenotype is characterized by male predominance, prevalence of cardiovascular symptoms during anaphylaxis, and low bone marrow mast cell proliferation [22]. These observations suggest that anaphylaxis in mastocytosis is not strictly dependent on mast cell burden but its severity and presentation are rather influenced by still incompletely defined phenotypes of the disease.

Cofactors in severe anaphylaxis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known triggers of anaphylaxis but they should also be considered a risk factor for severity of the reaction [25]. The mechanisms by which NSAIDs worsen anaphylaxis are not currently known but they are probably linked to the inhibition of cyclooxygenase and suppression of regulatory prostaglandins such as PGE2. In addition, NSAIDs may redirect arachidonic acid toward the synthesis of CysLTs that, as mentioned above, exert profound cardiovascular effects. Finally, NSAIDs may amplify the severity of food-induced anaphylaxis probably by augmenting gastrointestinal permeability.

Antihypertensive drugs have long been considered as cofactors of anaphylaxis mostly because it was thought that they would impair compensatory mechanisms activated during the reaction to support blood pressure. However, observational studies designed to understand the role of these drugs in anaphylaxis severity often gave conflicting results. Beta-blockers and ACE inhibitors, especially if taken together, may enhance the rate of a severe reaction. Besides blunting compensatory mechanisms, these classes of drugs have been shown to reduce the threshold of mast cell activation [26]. Patients taking beta-blockers are exposed to more severe reactions also because they are potentially resistant to epinephrine [25]. In a large cohort study, the use of all classes of antihypertensive drugs, including beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, and diuretics has been shown to increase organ system involvement and the risk of hospital admission for anaphylaxis [27]. However, although antihypertensive drugs augment the risk for severe anaphylaxis, they are rarely involved in fatal cases [12].

Alcohol intake is frequently listed as cofactor of severe anaphylaxis but data on its mechanism of action are lacking. Alcohol may be a potential risk factor for severe anaphylaxis because, through disinhibition, it increases the likelihood of accidental allergen exposure; it may hide early symptoms/signs of anaphylaxis and can suppress the physiological response to hypotension. Ethanol increases intestinal permeability to food allergens and regular alcohol consumers show higher levels of serum IgE as compared to the general population [7].

Exercise is a well-defined trigger of allergic disorders such as asthma, urticaria, and anaphylaxis. Exercise acts by increasing interstitial fluid osmolarity which in turn induces mast cell degranulation and release of vasoactive mediators. Moreover, physical exercise induces acidosis and raises body temperature

which further amplifies the reaction [8, 28]. Food-dependent exercise-induced anaphylaxis (FDEIA) is a specific pattern of anaphylaxis which can occur if exercise takes place a few hours after the ingestion of a specific allergen [28]. Multiple mechanisms have been proposed for FDEIA such as an increase in gastrointestinal permeability and allergen digestion, elevation of plasma IL-6, and, in the specific phenotype of gliadin-dependent exercise-induced anaphylaxis, the formation of large ω-5 gliadin/tTG complexes capable of eliciting anaphylactic reactions [29].

The role of *acute infections* as a risk factor for anaphylaxis has never been conclusively demonstrated. Fever may act by increasing blood circulation allowing a faster systemic distribution of allergens. Other mechanisms, such as those involving receptors on mast cells activated by bacterial or viral components (e.g., toll-like receptors), are not completely understood at this time [10].

Although male sex is considered a major risk factor, several studies demonstrate that anaphylaxis is more frequent in women than men during the reproductive period, suggesting that sexual hormones might play a role [30, 31]. Anaphylactic episodes occurring during *perimenstrual period* (*catamenial anaphylaxis*) may be due to different mechanisms. In some women, a hypersensitivity to endogenous progesterone has been demonstrated. In these patients, first sensitization may occur in relation to exogenous progesterone use and may be triggered by resensitization with endogenous progesterone during pregnancy. However, progesterone sensitization was not found in all patients with suspicious perimenstrual anaphylaxis. Another proposed trigger in these patients is represented by prostaglandins which are a constituent of menstrual fluid with vasoactive effects. In fact, PGF2 plays an important role in modulating mast cell mediator release and PGI2 (prostacyclin) is a powerful vasodilator. Estrogens might also play a role by enhancing endothelial expression of nitric oxide synthase and nitric oxide production, increasing vascular permeability, as it has been observed in a murine model [32, 33].

Table 1. Risk factors and cofactors of severe reaction according to anaphylaxis triggers

Drugs	Foods	Venom sting	Non-trigger-related cofactors/ risk factors
Old age (> 60 years)	Adolescence	MCDs	MCDs
Cardiovascular diseases	Exercise	Male sex	Exercise
Respiratory diseases	Uncontrolled asthma	Cardiovascular diseases	NSAIDs
Antihypertensive drugs	Alcohol consumption	NSAIDs	Alcohol consumption
		Antihypertensive drugs	Perimenstrual period
			Infections

MCDs mast cell disorders, *NSAIDs* nonsteroidal anti-inflammatory drugs
Physical exercise may be considered either a trigger or a risk factor

Uncontrolled asthma can be considered either a risk factor or a cofactor for severe anaphylaxis, especially food-induced. The higher incidence of food-induced anaphylaxis in patients with respiratory allergy may be explained by a phenomenon called "priming" which consists of an increase in number and reactivity of mast cells, basophils, neutrophils, and eosinophils in the airways of asthmatic patients during the pollen season. Such "armed" airways may be activated also by non-priming allergens (such as foods) and non-allergic stimuli. On the other hand, through the same mechanism, during the high pollen season, patients with food allergy may experience an increase of symptoms after the ingestion of allergenic foods. Asthma exacerbations are a well-documented event in most cases of food-driven anaphylaxis [12].

Patient risk factors and cofactors may differ from one age group to another and between different triggers, as shown in Table 1.

Conclusions

In spite of a large number of epidemiological studies, predicting factors for severe anaphylaxis are not fully elucidated. All major guidelines underscore the importance of defining patient-specific risk factors and cofactors to identify difficult-to-manage and potentially life-threatening reactions. Risk factors and/or cofactors are reported to be involved in about 20–30% of anaphylactic episodes [34, 35•].

Patient education and adequate treatment of comorbidities represent a central point of the anaphylaxis prevention plan and should be given the same importance of trigger identification. The impact of risk factors and cofactors on anaphylaxis outcome may be reduced by following a few rules:

- Avoid exposure to known allergens during treatment with NSAIDs
- Avoid exercise after exposure to known or suspected allergens (to be reinforced if associated to alcohol consumption or if NSAID treatment is ongoing)
- Maintain asthma control
- Develop specific action and prevention plans for old patients and for those with cardiovascular disease
- Evaluate for potential mast cell disorders in case of recurrent anaphylaxis (measure basal tryptase levels)

Further research is needed to find specific clinical and laboratory biomarkers useful to identify patients at risk for severe anaphylaxis.

Compliance with Ethical Standards

Conflict of Interest

Giulia De Feo, Roberta Parente, Chiara Cardamone, Tommaso Bucci, Ludovica Guerritore, and Massimo Triggiani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any study with human or animal subjects performed by any of the authors.

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- •• Of major importance

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