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Causes and risk factors for anaphylaxis

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Summary

Anaphylaxis is in most cases an IgE-dependent immunologic reaction. Mast cells are activated and release several mediators. Recent data about possible triggers of anaphylaxis indicate a clear age-dependency. The most frequent triggers of anaphylaxis in children are foods; in adults venom and drugs predominate. In 2006 an anaphylaxis registry was established in German-speaking countries. In the registry the triggers, circumstances, and treatment measures are collected from patients with anaphylaxis. However, the registry cannot supply epidemiological data like prevalence or incidence rates since the registration of cases is based on collaboration with allergy centers only. Similarly, other approaches to obtain data on the epidemiology of anaphylaxis are problematic given that allergic reactions of varying severity are covered by a number of codes in the ICD-10.

Research in the field of anaphylaxis is focused on the identification of risk factors. Several data indicate the relevance of co-factors and augmentation factors in well-defined patient groups. Among these factors physical activity, infection, alcohol and additives are relevant. In the future a unique coding system with a subtype analysis regarding the triggers and severity should help to provide data on the epidemiology of anaphylaxis. Furthermore the mechanisms of co-factors and identification of biomarkers for risk assessment are important research areas for the future.

Historical background and pathomechanism of anaphylaxis

Anaphylaxis was first described in 1902 by Richet and Portier who won the Nobel Prize in 1913 for physiology [1]. Their original intent was to scientifically prove the development of immune resistance to toxins from sea anemones. They injected dogs with an extract from the anemone, anticipating that after a second injection the dogs would develop immune-mediated protection to the toxins. Instead of immunological protection, however, the dogs had an immediate severe allergic reaction and died. They called this reaction “against” phylaxis (protection) – or anaphylaxis [2].

Although today these observations clearly suggest an IgE-dependent immediate hypersensitivity reaction, one must take into account that the discovery of IgE did not occur until much later in the 1960s made simultaneously by

Johansson and the husband and wife Ishizaka team [3]. Today anaphylaxis is defined as an immediate hypersensitivity reaction, which is mast-cell dependent and can vary in severity [4]. Based on the classification by Ring and Messmer, mild anaphylaxis is characterized by involvement of the skin and mucous membranes, while more severe forms involve the cardiovascular system and are potentially fatal (grade III–IV) [5] (Figure 1).

Although the majority of anaphylactic reactions are IgE-mediated and mast-cell dependent, there is discussion on the basis of animal studies as to whether IgG-mediated responses might also be significant [6–9]. In addition, along with mast cells, basophilic leukocytes may be involved in the development and severity of anaphylaxis [10]. More research is needed to clinically classify these findings. In addition to potential pathophysiological differences in anaphylaxis in terms of the triggering immunoglobulin class on the one hand and the cell types involved on the other, clinical data are increasingly

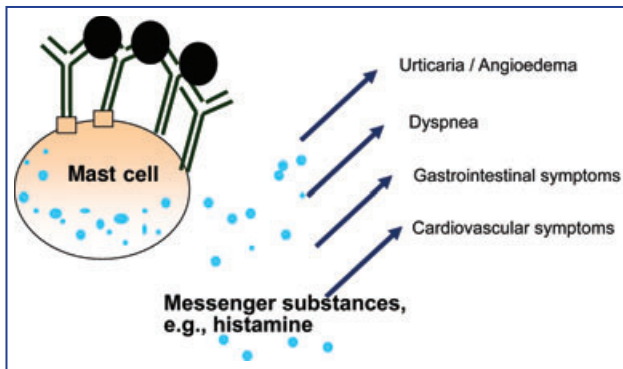


Figure 1 Pathomechanism of anaphylaxis.

suggesting that certain factors may promote the occurrence of an anaphylactic attack. Such co-factors, or augmentation factors, include infection, alcohol, physical athletic activity, and certain drug groups (e.g., non-steroidal anti-inflammatory drugs [NSAID]) [11]. The precise mechanisms by which these co-factors promote an anaphylactic attack are only partly understood and there is scant literature available at present [12, 13]. For the role of physical exertion, it has been suggested that increased gastrointestinal absorption of the allergen as well as re-distribution of the blood from the gastrointestinal tract to the muscles, as well as increased activity of relevant intestinal enzymes such as transglutaminase [14].

There is also increasing evidence that infection may be a co-factor in mast cell activation [15–17]. It is possible that direct activation of mast cells by bacterial components, e.g., LPS or lipoteichoic acid via toll-like receptors may play a role. Among drug co-factors, the pathophysiological role of NSAIDs has already long been established [18]. NSAIDs modify the cyclooxygenase enzyme activity profile (COX 1–2) and can thus both increase gastrointestinal tract permeability and aid in the development and triggering of anaphylaxis. Alcohol has also been discussed as a co-factor, presumably with a direct effect on gastrointestinal absorption, although the data are scarce [19]. Tryptase, which is released by mast cells, is detectable in the serum of patients 1 to 4 hours after a reaction. Unfortunately, it is not possible to detect it during the acute phase of an attack. Nevertheless, tryptase has a special role in the diagnostic work-up of anaphylaxis because increased levels ($> 20 \mu\text{g/l}$) raise suspicion of occult mastocytosis which also requires further diagnostic work-up [20]. For levels between the reference value ($11.5 \mu\text{g/l}$) and $20 \mu\text{g/l}$, further procedures must be decided on an individual basis. Rueff and colleagues demonstrated that patients with increased basal tryptase levels and insect venom allergy have an increased risk of severe anaphylactic reactions [21].

Other potential markers of anaphylaxis include serum levels of histamine and/or leukotrienes. These tests are not

routine and at the moment are only being performed in the framework of research projects.

Triggers of anaphylaxis

IgE-mediated reactions, and thus anaphylaxis, are usually triggered by proteins. The significance of having IgE antibodies to certain carbohydrates is currently being discussed. Anaphylactic responses have occurred in patients after administration of an antibody to the EGF receptor. Allergology studies showed that such patients have IgE antibodies to α -galactosidase (α -GAL) sugar. These α -GAL antibodies also appear to play a role in delayed allergic reactions to meat and proteins found in meat [22, 23].

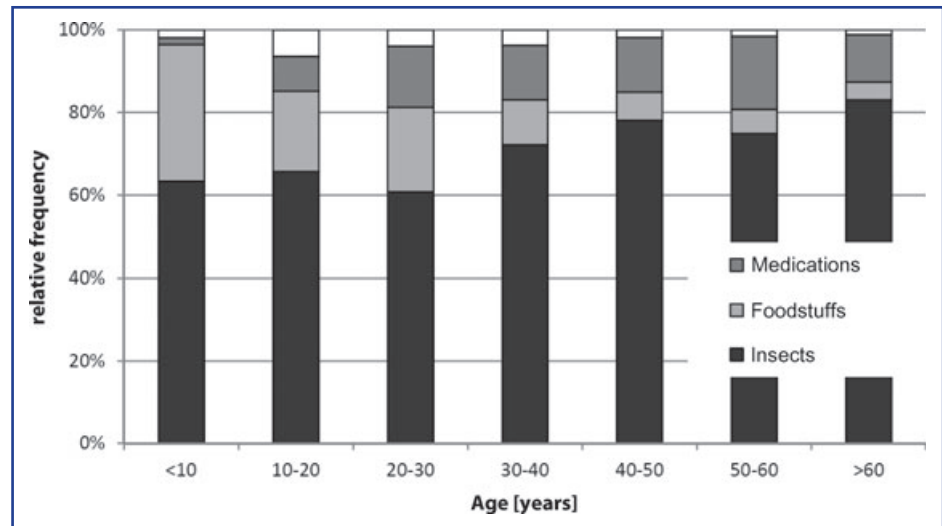
The frequency of the trigger varies depending on the age of the patient. Children are further divided into small children and adolescents. In young children, the most common triggers of food-related anaphylaxis are milk protein, hen's egg protein and wheat, while among adolescents peanuts and tree nuts are the most common triggers [11]. There are fundamental differences between the trigger profiles of foodstuffs in adults and children [24]. In adults the most common food allergens are wheat, celery and seafood [25]. In addition, co-factors contributing to the triggering of a reaction are more common in adults [24] (Figure 2).

Other important anaphylaxis triggers are insect venom and various medications. In Central Europe, the main insect triggers are bee and wasp venom [21, 26, 27]. Drug-induced anaphylaxis cannot be completely integrated pathophysiologically into the mechanisms described above. Along with IgE-mediated reactions, for instance, to penicillin, non-IgE-dependent reactions are also possible. Important triggers include non-steroidal anti-inflammatory drugs and numerous chemotherapy agents [28].

As already mentioned, the trigger profiles of anaphylaxis within the trigger groups (as described for foodstuffs) depend on age. The frequency of the trigger itself is also dependent on age. Insect venom allergy is a common trigger of severe allergic reactions in adults; but also drugs are common triggers of severe anaphylaxis in adults [25].

Finally, the order of the most common triggers of anaphylaxis is influenced by the study type. In one of our projects we observed that, in terms of the rank order of the trigger profile, patients who were treated by a paramedic more often had anaphylaxis due to an insect sting while in dermatologic practices, patients more often had an allergic reaction to specific immunotherapy [29]. In addition, even within certain medical specialties there are specific trigger profiles in terms of affected patients. Radiologists naturally see more contrast-media induced anaphylactic attacks while oncologists most often treat patients with anaphylactic reactions to chemotherapy [30].

Figure 2 Elicitors of anaphylaxis according to age; data from the anaphylaxis registry 2006–2012 (n=3144 cases).



It is important to track trigger profiles for anaphylaxis in order to create targeted schemes for prevention. It is also essential to promptly identify and report rare triggers. An example is lupine allergy which was first described in Norway [31]. After it was recognized as an important and relevant allergen in triggering severe allergic reactions, lupine flour was added to the declaration list of food allergens. Since then, the use of lupine flour has dramatically decreased and so has the number of patients with severe reactions to it.

In the German anaphylaxis registry, which was created in 2006, we document the trigger profile of anaphylaxis and can also promptly describe rare allergens as triggers of severe anaphylaxis. Thus for instance, in Germany in 2011 one patient had buckwheat allergy and another one had a parsnip allergy. Whether these allergens will increase and to what extent, is yet to be seen.

Risk factors for anaphylaxis

The risk factors for anaphylaxis vary and should be taken into account when seeing affected patients. In younger patients, peanut allergy is a risk factor for severe reactions. In patients with severe hypersensitivity, even minute amounts can cause severe or even fatal reactions. Just a few micrograms of peanut protein are enough [32]. Another important risk factor for anaphylaxis is age. With the aid of data from the anaphylaxis registry, we have shown that with increasing age the relative risk (odds ratio; OR) of severe cardiovascular symptoms (factor OR 6.06) increased dramatically [28]. When counseling patients with allergies, physicians should pay special attention to any accompanying cardiovascular diseases and ensure that patients are receiving appropriate care. In addition to cardiovascular diseases, pre-existing respiratory diseases also play an important role.

Several studies have shown that inadequate management of allergic bronchial asthma is an important risk factor for severe anaphylaxis [33, 34]. Mastocytosis patients also have an increased risk of anaphylaxis [35]. Patients with mastocytosis should thus always carry an emergency kit as a preventive measure, even if they have never experienced a severe reaction; the kit should contain an epinephrine auto-injector, a corticosteroid and an antihistamine [36, 37]. Increased tryptase has already been mentioned above as a risk factor for insect venom anaphylaxis. Data from epidemiological studies have shown that being male is a pre-disposing factor for insect venom anaphylaxis, among children as well as adults [21]. The reasons are as yet unknown, although IgE-mediated diseases are more common in boys up until puberty, while afterward they are equally common among boys and girls [38]. It is known that sex hormones can be involved in the development of the humoral immune response. Medications can also increase the risk of a severe allergic response. Among patients with insect venom allergy [21], it has been shown that simultaneous administration of ACE inhibitors and probably also beta blockers can negatively influence the severity of insect venom anaphylaxis. Other medications that likely play a role include aspirin and other non-steroidal anti-inflammatory drugs (Table 1).

One pathomechanism under discussion is an increased intake of allergens through the gastrointestinal tract. Yet mast cells can also be directly affected as effector cells by hormones. These and other mechanisms are believed to play an important role [38].

Epidemiology of anaphylaxis

Anaphylaxis occurs worldwide. Data have been published from various regions internationally. One article published in

Table 1 Co-factors and risk factors of anaphylaxis.

Lifestyle factors	Drugs	Pre-existing diseases	Patient-specific factors
Physical exertion	COX 1/2 inhibitors	Increased basal Tryptase	Sex, advanced age
Added substances	ACE inhibitors	Mastocytosis	Sex, advanced age
Alcohol	β -blockers	Bronchial asthma	Active infections

Table 2 Advantages and limitations of clinical epidemiology.

Advantages	Limitations
▶ Well-characterized sample	▶ No data on prevalence and incidence
▶ Suitable for rare diseases	▶ Not representative of the population

the United States reported an incidence of 50 out of 100,000 inhabitants, while in Great Britain the reported rate is about 8 out of 100,000 [39, 40]. Possible causes of the differences include a lack of uniform ICD codes for anaphylaxis and the fact that several ICD codes are taken into account when calculating the incidence rates. Nevertheless, these articles and others mention that anaphylaxis has been steadily rising in industrialized nations in the past 20 years [25, 41, 42]. Due to the lacking uniformity in data collection, there are still no completely reliable epidemiological data on anaphylaxis. Given its rarity, a study at the population level would take a massive effort. In our own study for the Berlin region, in collaboration with Berlin emergency doctors, who completed a standardized survey for each patient treated for an anaphylactic reaction, we calculated an incidence rate of 2.5 out of 100,000 inhabitants in 2008 [43]. It is important to note that only those patients were included who had severe allergic reactions, i.e., with respiratory and/or cardiovascular symptoms. Anaphylaxis can also occur in hospitals during diagnosis or treatment, and such occurrences would not have been included in the survey.

It was because of this limitation in the collection of epidemiological data on anaphylaxis that the anaphylaxis registry was created (Network for Online-Registration of Anaphylaxis – NORA e. V.). The project is based on the collaboration with various allergy centers across Germany, Austria, and Switzerland (www.anaphylaxie.net). The data are collected online via a password-protected site. As a clinical epidemiology instrument, the anaphylaxis registry includes only affected patients from allergy centers. Thus these data cannot be used for information on the incidence

or prevalence of the disease (Table 2). Nevertheless, they allow for a description of demographic features (age and sex of affected patients), as well as data on co-morbidities (e.g. atopic diseases or mastocytosis), diagnosis, and treatment [44]. Even if only a portion of affected anaphylaxis patients is included, the system offers the advantage of high-quality data from registered patients on patient history and diagnostic work-up by the allergy specialist. A recently initiated study on the validity of the data in the anaphylaxis registry showed that the survey questions display a high level of quality.

Perspectives

Anaphylaxis is a rare disease. Given that it can be fatal, it is a particular challenge for doctors who treat patients with allergic diseases. Patients must be diagnosed to identify the triggers and they must be thoroughly educated about the disease how to manage it with emergency medications. Ideally, patients should be instructed in the framework of a standardized programs such as have been developed and established by AGATE e. V. (Working Group on Anaphylaxis Training & Education). Affected patients, or the parents of underage children, should be informed as to where triggers may be present in everyday life and how to avoid them [45]. Another important element of the anaphylaxis management is prescribing an emergency kit in accordance with the guidelines on the management of anaphylaxis [37]. Here, too, patients need to be thoroughly informed about the correct usage of the drugs which have been prescribed including the correct use of the adrenalin autojector.

More research is needed into the pathophysiology, as well as the mechanistic importance of co-factors for triggering an anaphylactic reaction. The anaphylaxis registry can contribute to this at the level of clinical epidemiology. Given that uniform ICD codes for anaphylaxis have not yet been established (i.e., various triggers are listed such as foodstuff anaphylaxis [ICD T78.0] and insect venom hypersensitivity [ICD T63.4]), it would be desirable to use standardized codes, with suitable sub-groups, in order to obtain specific epidemiological data on anaphylaxis.

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