



# Update on the understanding, diagnosis and tailored management of anaphylaxis: making progress

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Anaphylaxis affects 0.5–2% of general population lifetime and it is the most severe allergic condition. The frequency of anaphylaxis-related deaths ranges from 0.3 to 0.8 per million of inhabitants. An increasing trend of its incidence has been recently reported [1]. Impressive improvements in the knowledge of its pathogenesis, as well as in the diagnostic and therapeutic workup, have been very recently reported and are highlighted in the present issue.

The cardiovascular involvement has a key role in the prognostic outcome of any episode of anaphylaxis. The presence of mast cells located within the adventitia of the large coronary vessels and their mediator release (histamine, leukotrienes, platelet activating factor, chimase, etc.) during the allergic reaction can strongly affect the coronary blood flow, the myocardial function and the cardiac rhythm. Preexisting cardio-ischemic disease is a crucial negative risk factor in patients during an anaphylactic episode. On the other hand, severe cardiac ischemia, as in the variant I° of Kounis syndrome, is possible in patients without a preexistent coronary disease. This strong relationship between heart and anaphylaxis leads to a regular cooperation between cardiologists and allergists. In fact, any patient at risk of anaphylaxis relapse, especially if elderly, should be checked for cardiac risks, particularly in patients with ischemic cardiovascular diseases. Also, the choice of the antihypertensive treatment is a critical issue as virtually every antihypertensive drug has been demonstrated to be a risk factor in patients with anaphylaxis, besides beta-blockers and angiotensin converting enzyme inhibitors [2]. Additionally, the use of epinephrine can be a risk in patients with preexisting cardiac diseases.

Even if anaphylaxis is considered the paradigm of IgE-mediated disease, the mere detection of specific IgE is sometimes not sufficient for the development of anaphylaxis, which needs the contribution of other factors. In addition to the affinity and the serum concentration of specific IgE, the nature of the culprit allergen has a critical role.

Consequently, the recent availability of the Component Resolved Diagnosis (CRD) has enabled impressive progress in the risk assessment of anaphylaxis. In fact, component testing contributes to the identification of the pattern of sensitization at a molecular level, connecting the clinical response to this pattern and discriminating the primary sensitizations from the cross-reactivity [3]. The potential of CRD is particularly relevant in food allergy [4]. Proteins which are stable to heat and acid, such as the prolamin superfamily (alpha amylase and protease inhibitors), storage proteins (2S albumin), nonspecific lipid transfer protein (LTP) and the protein family of cupins, have a high anaphylactic potential [5]. PR 10 proteins which are not stable to heat and acid and are relevant cross-reacting components in many allergen extracts are responsible for oral allergy syndrome, and are less likely to be associated with generalized symptoms. Different patterns of sensitization have been observed according to different geographical areas and ages. LTP is the most common allergen responsible for anaphylaxis in the Mediterranean countries [5], whereas sensitization to PR 10 proteins is more common in the northern Europe and the United States. Similarly, in peanut allergy, sensitization to Ara 1/2/3 proteins is predominant in the United States, whereas in Europe, sensitization to Ara9/LTP is more commonly seen [6]. According to the age, sensitization to milk, egg and wheat are common in children, whereas seafood, nuts and celery are more frequent allergens eliciting anaphylactic reactions in adults. CRD is also useful in detecting the sensitization to minor allergen. This is the case of the

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sensitization to omega-5 gliadin or to a lesser extent  $\alpha/\beta/\gamma$  gliadin, a marker of wheat-dependent exercise-induced anaphylaxis [7]. This clinical variety of anaphylaxis, whose incidence is increasing, is a paradigm of the critical role of cofactors for the development of the anaphylaxis. In addition to exercise, whose provocative threshold is different from patient to patient, aspirin, through the impairment of the tight junctions, can increase the absorption of the culprit allergens and, therefore, increase the allergen uptake. Additionally, alcohol consumption shares the same mechanism in facilitating the anaphylactic reaction. Infection can be a relevant cofactor as well, through cellular activation by immune innate receptors [8].

In addition to the diagnosis of food allergy, CRD has impressively improved the specificity and sensitivity of the Hymenoptera venom diagnosis. The availability of recombinant Ves v 5 or Ves v1 has identified sensitized patients, who previously have been negative to the commercial extracts. In addition, CRD could be useful in polysensitized patients as it can discriminate the primary sensitization from cross-reaction because of cross-reactive carbohydrate determinants [9]. An appropriate diagnosis based on the CRD results could also reduce the risk of overtreatment in Hymenoptera-allergic patients and consequently the costs of their management. As discussed by Golden [10] in this edition, promising data are coming from the use of the basophil activation test (BAT) in patients with positive history and negative tests for venom extracts. Furthermore, preliminary data suggest a potential utility of CD63 BAT in deciding when to discontinue venom immunotherapy, thus further reducing the costs [11].

In addition to the costs, immunotherapy for venom and inhalant allergy share the problem of safety. Before 2009, the risk of fatality for venom and inhalant allergy was 1 in 1 million. However, no fatalities have been reported in the United States in the last 2 years, thereby further lowering the risk. The inconvenience of traveling to the clinic is one of the most important reasons for poor adherence to the treatment; therefore, rush and cluster schedule may be preferred to the traditional protocol for advancing immunotherapy. Interestingly, cluster schedules for inhalant allergy are reported to have a rate of systemic reaction similar to the traditional and longer schedules [12]. Rush immunotherapy for both venom and aeroallergens is responsible for a higher frequency of systemic reaction. Sublingual immunotherapy (SLIT) is widely used in Europe and has now been approved in the United States. The

safety profile of SLIT is quite high, with no fatalities being reported to date. However, anecdotal cases of anaphylaxis with SLIT have been published, usually related to the use of nonstandardized extract or to inappropriate practice. It is, therefore, advisable to administer the first dose under medical supervision. Finally, in very select cases of patients at high risk of anaphylaxis during immunotherapy, the use of omalizumab may be a consideration. A careful evaluation of the cost and benefit analysis is warranted in these cases.

In conclusion, a better understanding of the mechanisms underlying the development of anaphylaxis, the clearer identification, the recognition of the role of cofactors and risk factors, and the detection of the single pattern of sensitization have recently permitted an impressive improvement of the clinical approach to the anaphylaxis, leading to the possibility of providing tailored management to each individual patient.

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## Conflicts of interest

*There are no conflicts of interest.*

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