

Anaphylaxis in children

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Abstract

Anaphylaxis in children is a potential acute life-threatening systemic hypersensitivity reaction. Anaphylaxis fatality rate is estimated to be 0.65% to 2%. Food is the main anaphylaxis trigger in children, notably cow's milk, peanuts, and tree nuts. Mucocutaneous manifestations are observed in more than 90% of cases, but it is not essential for diagnosis. Deaths are rather secondary to the laryngeal edema, observed in 40%-50% of cases. Personal history of asthma, allergy to particular foods such as peanuts and tree nuts, and adolescence are known risk factors for anaphylaxis and more severe reactions. Epinephrine (adrenaline) is the medication of choice for the first-aid treatment of anaphylaxis. However, adrenaline auto-injectors (AAIs) are commercially available in only 32% of world countries. There are still considerable unmet needs in the field of anaphylaxis in children. Therefore, the Montpellier WHO Collaborating Centre aims to start the global action plan applied to anaphylaxis.

KEYWORDS

adrenaline/epinephrine auto-injectors, anaphylaxis, classification, epidemiology, management, prevention, treatment

Anaphylaxis in children is a potential acute life-threatening systemic hypersensitivity reaction characterized by rapid onset and the potential to endanger life through airway, breathing, or circulatory problems. It is usually, although not always, associated with skin and mucosal changes.¹ Its heterogeneous clinical presentation and sudden occurrence in virtually any setting without warning hamper the prompt recognition and treatment of this condition, increasing the risk of death.

Epinephrine (adrenaline) is the medication of choice for the first-aid treatment of anaphylaxis. However, adrenaline auto-injectors (AAIs) are only commercially available in only 32% of world countries.²

Trends in anaphylaxis epidemiology are often assessed using health data relating to anaphylaxis admissions. For instance, in Europe, the lifetime prevalence of anaphylaxis is estimated to be 0.3% (95% CI 0.1-0.5).³ Hospitalisations due to anaphylaxis are also increasing in many countries, in particular in young children; these increases are noted particularly for medication and food triggers.⁴

Anaphylaxis is a recognized cause of death in all ages, and anaphylaxis-related mortality rate is less than 1 per million per year in most high-income countries. However, this estimate is likely to be lower than the true rate of fatal anaphylaxis, due to under-diagnosis and under-notification. Besides, there are limited epidemiological data from middle- and low-income countries. One of the recognized difficulties in reaching accurate anaphylaxis data in population-based studies is the misclassification of this condition under the World Health Organization (WHO) International Classification of Diseases (ICD), but may gain new perspectives thanks to the implementation of the ICD-11, in which a pioneer chapter addressed to allergic and hypersensitivity conditions has been built.^{5,6}

Food is the main anaphylaxis trigger in children, notably cow's milk, peanuts, and tree nuts,⁴ but the main potential food triggers can differ in different countries and world regions depending on the food consumption pattern. The highest rates of non-fatal food-induced anaphylaxis occur in young children, but fatal outcomes are rare in this age-group.⁵ The greater risk appears to be in adolescence

and young adulthood. The most frequent food allergens involved in lethal anaphylaxis at any age are peanut and tree nuts, accounting for 55%-87% of deaths. However, other allergens are also implicated. The majority of fatal food anaphylaxis occurs in individuals known to be food-allergic; less than half have received before a prescription of an AAI.⁴

Antibiotics, and particularly beta-lactams, have been identified as the main cause of drug-induced anaphylaxis in children. Non-steroidal anti-inflammatory drugs are at the second rank as triggers of pediatric drug-induced anaphylaxis. The data are probably related to the high prescription rates of these drugs.⁷

Stings from insects of the order Hymenoptera (bees, wasps, and ants) are the most common cause of insect-related anaphylaxis. However, the proportion of children allergic to insect bites or sting who develop anaphylaxis is lower than that of insect allergic adults.⁸

Recently, the World Allergy Organization (WAO) Anaphylaxis Committee revised the diagnostic criteria for anaphylaxis as reported in Table 1.⁹

Vomiting, urticarial, and laryngeal edema are more frequent at this age-group. Mucocutaneous manifestations are observed in more than 90% of cases, but it is not essential for diagnosis. Deaths are rather secondary to the laryngeal edema, observed in 40%-50% of cases. Cardiovascular involvement is rare in infants, most often observed in adolescents, probably related to age-dependant physiological changes. The time to onset of food anaphylaxis after oral exposure is on average 30 minutes (5 minutes-2 hours), more rarely beyond.

Recently, a study suggested a distinct food-induced anaphylaxis phenotype when compared infants (≤ 12 months) to pre-school

Key message

Although uncommon, fatal anaphylaxis in children is mostly related to food accidental exposure in patients with known allergy and, therefore, preventable.

children (1-6 years). Infants presented as their first anaphylaxis triggered by cow's milk and manifested more hives, hypotonia, and hypotension than pre-school children.¹⁰

There are unusual clinical forms of anaphylaxis in childhood, such as exercise-induced anaphylaxis, anaphylaxis linked to allergy to alpha-galactose, which should be investigated when suspected.

Personal history of asthma, allergy to particular foods, such as peanuts and tree nuts, and adolescence are known risk factors for anaphylaxis and more severe reactions. History of asthma is present in more than two-thirds of cases of food-induced anaphylaxis in children and may explain the tendency of fatal food-related anaphylaxis to primarily be due to bronchospasm and laryngeal angioedema, with cardiovascular collapse generally occurring secondary to hypoxia and respiratory arrest.⁴

Since adrenaline administration by intramuscular route is the life-saving patients suffering with anaphylaxis, guidelines state the prescription of AAI in all cases in which the trigger cannot be avoided, such as in drug-induced anaphylaxis. In countries in which AAI are available, the 0.15 mg dose is recommended to children weighting 15-30 kg. In 2018, in United States, the Food and Drug Administration has approved a 0.10 mg dose AAI for children weighing 7.5-15 kg. Further studies designed to evaluate the efficacy and tolerability of lower dose, and optimal needle length of AAI in infants weighting <7.5 kg are still required.¹⁰

Most of cases of anaphylaxis are first seen by emergency doctors, pediatricians, or general practitioners. However, only about 50% of patients are referred to allergists for further investigation and/or treatment. Strengthening the collaboration among specialties is crucial for the quality management of anaphylactic patients.

Specific improvements have been observed in the field of anaphylaxis such as the regular food allergens information in labels and in different establishments such as schools and restaurants and national and international allergy organizations have produced a number of anaphylaxis guidelines. However, besides all the efforts, we still face a relevant number of unmet needs to be managed in the forthcoming years.

In June 2018, the WHO Collaborating Center (WHO CC) for the Scientific Classification of Allergic and Hypersensitivity Diseases was established at the University Hospital of Montpellier, headed by LKT and PD.¹¹ This designation is the result of recognition by WHO of all the efforts of the *ALLERGY in ICD-11 initiative*. As the only WHO Collaborating Center for classifications of allergic and hypersensitivity conditions, we intend to establish close collaboration with national bodies in order to implement actions for better patients' care, monitor and prevention, and developments in research and launch

TABLE 1 Diagnostic criteria for anaphylaxis revised by World Allergy Organization

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **AND AT LEAST ONE OF THE FOLLOWING**:
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
 - c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotension* or bronchospasm or laryngeal involvement^a after exposure to a known or highly probable allergen^b for that patient (minutes to several hours^c), even in the absence of typical skin involvement.

Abbreviations: BP, blood pressure; PEF, Peak expiratory flow.

i. Infants and children under 10 years: systolic BP less than (70 mm Hg + [2 × age in years]).

ii. Adults: systolic BP < 90 mm Hg.

*Hypotension defined as a decrease in systolic BP > 30% from that person's baseline, OR.

The aim of using superscript letters is to differentiate data from children and for adults.

measures in order to reduce avoidable deaths. Our WHO CC will provide the means through which governmental and non-governmental collaborating parties can combine their strengths to achieve focused objectives, avoiding wasting energy and resources.^{2,8} Our aim is starting the action plan applied to anaphylaxis as a model, but we may extend to other allergic and hypersensitivity conditions in the coming period. Human and financial resources will be required and may be achieved through the support from the mentioned bodies involved, robust research projects, and structured collaborations. We intend to take all the support to move on the proposed action plan. For that, structured collaborations are under construction. Essential is aligning international and national efforts for increasing awareness and strengthening the collaboration structured efforts among professionals dealing with anaphylaxis.²

CONFLICT OF INTEREST

The authors declare that they do not have conflict of interests related to the contents of this article.

AUTHOR CONTRIBUTIONS

Luciana Kase Tanno: Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Pascal Demoly:** Data curation (equal); Writing-review & editing (equal).

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