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Anaphylaxis (M Sanchez-Borges, Section Editor)

Childhood Anaphylaxis: State of the Art

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Abstract

Purpose of the Review Anaphylaxis is a systemic immunologic reaction of immediate hypersensitivity that occurs as consequence of an interaction between antigen and immunoglobulin E (IgE) and may be potentially fatal. Anaphylaxis symptoms usually occur minutes or seconds after the exposure to the causing allergen. The sooner the reaction is established, the more severe it is. The main causes in children are food (cow's milk, peanut, egg) and insect bite. Its clinical manifestations usually vary. They can be mild, presenting with hives, angioedema, abdominal pain; or severe, presenting with hypotension or shock, and there may be a late phase reaction. The first-line treatment for anaphylaxis is intramuscular epinephrine. The use of anti-histamines and corticosteroids is controversial.
Recent Findings The presence of hypotension is predictive of additional epinephrine administration.
Summary All cases must be evaluated by an allergist. In addition to preventive measures, patients and their families need to be educated on how to manage anaphylactic reactions.

Introduction

Anaphylaxis is a systemic immunologic reaction of immediate hypersensitivity that occurs as consequence of an interaction between antigen and immunoglobulin E (IgE) fixed on basophils and mast cells. Anaphylactic reactions are contemporaneous diseases, with case series reported in the first decades of the twentieth century with the advent of immunobiological agents (such as heterologous antitetanus serum) and in the second half of the century, with drugs, diagnostic agents, foods, insect venom, and exercise [1].

Anaphylaxis risk in childhood cannot be precisely estimated because data are scarce and present methodological weaknesses [2••, 3••, 4•, 5].

Despite anaphylaxis being a medical emergency, there is scarce information about its prevalence and characteristics, particularly in children. Doctors, especially those who work in emergency departments, should be prepared to recognize and treat the event, which may be fatal in some cases [6].

Pediatric emergency department (ED) visits for children with anaphylaxis have increased from 5.7 to 11.7 per 10,000 visits from 2009 to 2013, and the overall burden of childhood allergic disease is increasing [7]. The severity of anaphylaxis also might be worsening, as observed in a US database of anaphylaxis-related emergency department visits [8••].

Anaphylaxis initiates suddenly and unexpectedly. Its severity varies and it may resolve spontaneously. The overall death rates due to anaphylaxis are low [8••]. Its course is unpredictable in children [9•].

Mechanisms

Type 1 immediate hypersensitivity reaction requires the presence of specific IgE antibodies fixed to high affinity receptors on mast cells and basophils membrane; and the consequent release of potent pharmacologic substances, like histamine, tryptase, platelet-activating factor (PAF) and leukotrienes [10]. Platelet-activating factor is a phospholipid mediator with central role in anaphylaxis. It is rapidly metabolized by acetyl-hydrolase, and its activity inversely correlates to the severity of the reaction [11].

Those chemical mediators cause systemic vasodilation, increased capillary permeability, bronchoconstriction, arterial hypotension, and shock. Paradoxically, histamine may cause coronary arteries vasoconstriction, which may lead to myocardial ischemia, especially if atherosclerosis is present. Impending death sensation, generalized pruritus, diffuse erythema (flushing), and tachycardia may progress to syncope, with or without arterial hypotension [1, 4•].

Anaphylaxis symptoms usually occur minutes or seconds after the exposure to the causing allergen. The sooner the reaction is established, the more severe it is. There is a correlation between serum-specific IgE antibody levels and the rapidity of the development of immediate cutaneous reaction due to antigenic stimulus [12].

Etiology

The main causes of anaphylaxis in children are food and insect bite. Other causes are displayed in Table 1 [12–14].

Table 1. Causes of anaphylaxis in children

Foods	Cow's milk, egg white, peanut are the most frequent.
Insects	Hymenoptera (bees, wasps, ants); rarely bugs and mosquitoes.
Drugs	Antibiotics, non-steroidal anti-inflammatories, and antipyretics are the most common. Any drugs may induce allergic reaction.
Other causes	Physical exercise, vaccines, immunobiologicals, allergen immunotherapy, local and general anesthetics, muscle relaxants, latex, chlorhexidine, idiopathic, etc.

Most substances causing anaphylaxis are proteins. However, polysaccharides may also be allergenic. A survey performed in Latin America demonstrated that the most frequent etiologic agents of anaphylaxis in children younger than 4 years old were cow's milk (41%) and ant bites (36%); between 4 and 8 years old ant bites (64%) and peanut (27%); and older than 8 years, non-steroidal anti-inflammatories (38%) and bee stings (31%) [5, 15].

Clinical features

Anaphylaxis onset and course may vary between patients and in the same person. There is a combination of symptoms and they may not be present at the same time.

Laryngeal edema and cardiovascular collapse are the leading causes of death during allergic reactions. Arterial hypotension and tachycardia are severity signs in anaphylaxis. Urticaria (hives) and angioedema are the most common clinical manifestations of anaphylactic reactions, but may not occur in some cases [5].

Acute urticaria should be evaluated as initial manifestation of anaphylaxis and should be treated as such, because it may progress to the other symptoms and signs in a matter of minutes. The risk of new anaphylaxis episodes is greater if there is a personal history of atopic dermatitis, urticaria, and/or angioedema and positive skin prick tests to at least one food allergen [16••]. Vomiting, diarrhea, and abdominal pain are gastrointestinal manifestations of anaphylactic reactions [1].

Upper airway obstruction is characterized by dysphonia, barking cough, stridor, and swallowing difficulty. Lower airway involvement encompasses wheezing, cough, and dyspnea (Table 2). It is more likely that the asthmatic patient wheezes during anaphylaxis than the non-asthmatic. Death in systemic reactions occurs more often in patients with non-controlled asthma. Previous anaphylaxis and asthma are indicators of severity in food allergy. On the other hand, it is difficult to predict those who have lower risk of severe reactions [1, 2••, 3••]. Respiratory symptoms are more common in children, whereas cardiovascular symptoms more often occur in adults [17, 18].

Anaphylactic reactions may have an immediate phase and, hours after the recovery, a late phase, with recurrence of symptoms. These biphasic reactions may be fatal and occur in up to 20% of the cases, approximately 8 h after the

Table 2. Clinical manifestations of anaphylaxis

Mucocutaneous	Pruritus, hives, angioedema, diffuse erythema (flushing)
Respiratory	Rhinitis, asthma, cough, stridor, laryngeal edema
Cardiovascular	Tachycardia, hypotension, arrhythmias, syncope
Gastrointestinal	Vomiting, diarrhea, abdominal pain
Others	Seizures, amaurosis, dizziness, imminent death feeling

initial presentation. The clinical impact of these biphasic reactions is on the period of observation, which is mandatory after treating, to avoid relapse after discharge [1, 4•].

Diagnosis

Anaphylaxis diagnosis is highly probable when one of the following three criteria is fulfilled:

1. Sudden onset reaction in minutes or hours with cutaneous and/or mucous involvement (hives, pruritus, flushing, angioedema) with at least:
   a. Respiratory symptoms (dyspnea, wheezing, stridor, hypoxemia);
   b. Arterial hypotension and its symptoms (hypotonia, syncope, sphincter incontinence, shock).
2. Two or more of the following after exposure to a known allergen:
   a. Hives, pruritus, flushing, angioedema;
   b. Respiratory symptoms;
   c. Symptomatic hypotension;
   d. Gastrointestinal symptoms.
3. Arterial hypotension after exposure to a known allergen [1, 2••, 19•, 20].

The diagnosis of anaphylaxis is clinical. The evaluation of the patient should be quick, based in the medical history and physical examination during the reaction, including signs of airway obstruction, arterial hypotension, and cutaneous symptoms.

High serum tryptase levels help to confirm the anaphylactic nature of the reaction if assessed within 2 h after the event, and may be predictive of anaphylaxis risk in children allergic to food [16••, 21, 22••]. IgE-specific antibody detection can be done by skin prick testing or quantitative serum analysis by fluorescence enzyme immunoassay [22••].

A new proposal classifies the severity of the allergic reaction in three types, from isolated cutaneous manifestations to the complete anaphylactic reaction spectrum. However, further discussion is necessary, especially in pediatric allergy [23].

Evaluation by an allergist is mandatory for the etiologic diagnosis of anaphylaxis and must include a detailed medical history and search for possible triggers of the reaction (foods, drugs, insect stings, activities) [2••, 11, 20].

Differential diagnosis of anaphylaxis includes vasovagal syncope, diffuse erythema, carcinoid syndromes, autonomic epilepsies, and food poisoning. Patients with repeated anaphylactic reactions with or without identified cause must be investigated for systemic mastocytosis. High serum tryptase levels in asymptomatic periods that increase even more during attacks may suggest the diagnosis of mastocytosis [1, 2••, 11, 19•, 20].

Management

Anaphylaxis treatment should consider the severity of the reaction and the time since onset. The main objectives of treatment are to keep the airways patent,

offer supplementary oxygen, re-establish intravascular volume, and stabilize cardiorespiratory conditions [20, 21].

Mild forms, presenting with urticaria/angioedema and any other symptom (cough, vomiting, wheezing, diarrhea), may be treated with intramuscular (IM) epinephrine, oral second-generation anti-H1 anti-histamines, inhaled beta-2 agonists, and oral corticosteroids. The patient should be kept in the hospital for at least 4 h, because the reaction may progress to more severe forms. If the only symptom is urticaria (hives), the use of epinephrine is controversial, even though it is recommended in face of a previous history of anaphylaxis.

Severe forms, presenting with respiratory distress, arterial hypotension, syncope, and cardiac arrest, should be promptly treated with oxygen, intravenous (IV) reposition of fluids with saline solution or plasma expanders, IM epinephrine, IV corticosteroids, and anti-H1 and anti-H2 anti-histamines. It is crucial to keep the patient in Trendelenburg position. Epinephrine can be administered by inhalation for laryngeal edema.

Corticosteroids should not be the first treatment option, since their onset of action is not prompt to relieve acute and critical manifestations. Systemic corticosteroids are indicated in prolonged shock, laryngeal edema, refractory bronchospasm, and late phase reactions. Anti-H1 and anti-H2 anti-histamines and glucagon have not been adequately studied in children. Intramuscular epinephrine is the initial standard treatment for anaphylaxis. If there is no response to IM epinephrine, it can be used intravenously with the patient carefully monitored [4•, 7, 19•, 21]. The presence of hypotension is a predictive of repeated epinephrine administration [24•].

Management After Discharge from the Emergency Room and Prevention

Once the patient is discharged from medical care, the child and family should be instructed to observe late phase reactions, avoid potential triggers, recognize initial manifestations of anaphylaxis and, in some cases, have epinephrine self-injectors.

The child should be evaluated by a specialist (allergist) to elucidate possible triggers, formulate action plans, and treat any comorbidities.

Conclusions

Anaphylactic reactions are emergencies in allergy and may be triggered by different agents, such as drugs, foods, and insect venom, especially in childhood.

Urticaria may be the first sign of anaphylaxis. Initial mandatory treatment of anaphylaxis is intramuscular epinephrine. Prolonged hospital observation allows identification and management of late phase reactions.

All patients with anaphylaxis must be referred to an allergist to evaluate risk of future reactions, comorbidities, and possible treatments. In addition to preventive measures, patients and their families need to be educated on how to manage anaphylactic reactions and have training in the use of epinephrine auto-injectors and written emergency plans [25, 26•].

Compliance with Ethical Standards

Conflict of Interest
Cristine Rosario and Nelson Rosario Filho declare no conflicts of interest relevant to this manuscript.

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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Simon GA, Brown SGA, Kemp SF, Lieberman PL. Anaphylaxis. In: Adkinson Jr NF, Bochner BS, Busse WW, Holgate ST, Lemanske Jr RF, Simons FER, editors. Middleton's allergy: principles and practice. 8th ed. St Louis: Mosby, Inc; 2014. p. 1027–49.
2.•• Muraro A, Roberts G, Worm M, Biló MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014;69:1026–45. https://doi.org/10.1111/all.12437

This is an important guideline for anaphylaxis diagnosis and treatment.

3.•• Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015;8:32. https://doi.org/10.1186/s40413-015-0080-1

A complete guideline written by the World Allergy Organization Anaphylaxis Committee.

4.• Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis: a practice parameter up-date 2015. Ann Allergy Asthma Immunol. 2015;115:341–84. https://doi.org/10.1016/j.anai.2015.07.019

A very useful update, focused on clinical practice aspects.

5. Solé D, Ivancevich JC, Borges MS, Coelho MA, Rosario NA, Ardusso LRF, et al. Anaphylaxis in Latin America: a report of the online Latin American survey on anaphylaxis (OLASA). Clinics (Sao Paulo). 2011;66:943–7. https://doi.org/10.1590/s1807-59322011000600004.
6. Bernd LAG, Sá AB, Watanabe AS, Castro APM, et al. Anafilaxia: guia prático para o manejo da anafilaxia. Rev Bras Alerg Imunopatol. 2012;35:53–70.
7. Farbman KS, Michelson KA. Anaphylaxis in children. Curr Opin Pediatr. 2016;28:294–7. https://doi.org/10.1097/MOP.0000000000000340.
8.•• Miller RL, Shtessel M, Robinson LB, Banerji A. Advances in drug allergy, urticaria, angioedema, and anaphylaxis in 2018. J Allergy Clin Immunol. 2019;144:381–92. https://doi.org/10.1016/j.jaci.2019.06.010

Most recent update on anaphylaxis.

9.• Pouessel G, Antoine M, Lejeune S, Dubos F, Pierache A, Deschildre A, et al. The time course of anaphylaxis manifestations in children is diverse and unpredictable. Clin Exp Allergy. 2019. https://doi.org/10.1111/cea.13510

It is important to understand the heterogeneity of anaphylaxis manifestations in children.

10. Panesar SS, Javad S, De Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013;68:1353–61. https://doi.org/10.1111/all.12272.
11. Simons FER, Clark S, Camargo CA Jr. Anaphylaxis in the community: learning from the survivors. J Allergy Clin Immunol. 2009;124:301–6. https://doi.org/10.1016/j.jaci.2009.03.050.
12. Gill P, Jindal NL, Jagdis A, Vadas P. Platelets in the immune response: revisiting platelet-activating factor in anaphylaxis. J Allergy Clin Immunol. 2015;135:1424–32. https://doi.org/10.1016/j.jaci.2015.04.019.
13. Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2013. J Allergy Clin Immunol. 2014;133:324–34. https://doi.org/10.1016/j.jaci.2013.11.013.
14. Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M. Anaphylaxis in an emergency setting – elicitors, therapy and incidence of severe allergic reactions. Allergy. 2012;67:1451–6. https://doi.org/10.1111/all.12012.
15. Hompes S, Kohli A, Nemat K, Scherer K, Lange L, Rueff F, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents – data from the anaphylaxis registry of German-speaking countries. Pediatr Allergy Immunol. 2011;22:568–74. https://doi.org/10.1111/j.1399-3038.2011.01154.

16.•• Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical immunology. Allergy. 2007;62:857–71. https://doi.org/10.1111/j.1398-9995.2007.01421.x

Position paper to establish anaphylaxis management in children.

17. Sahiner UM, Yavuz ST, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Tuncer A, et al. Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy. Allergy. 2014;69:265–8. https://doi.org/10.1111/all.12317.

18. Chong Neto HJ, Rosario NA. Studying specific IgE: in vivo or in vitro. Allergol Immunopathol. 2009;37:31–5.

19.• Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Diagnosis and management of food allergy. Allergy. 2014;69:1008–25. https://doi.org/10.1111/all.12429

Important to understand the association between food allergy and anaphylaxis.

20. Arroabarren E, Lasa E, Joral A, Pérez-Yarza EG. Managing pediatric anaphylaxis. US Respir Dis. 2012;8:23–9.

21. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilo B, et al. Management of anaphylaxis: a systematic review. Allergy. 2014;69:159–67. https://doi.org/10.1111/all.12314.

22.•• Simons FER, Ardusso LRF, Bilo MB, ElGamal YM, Ledford DK, Ring J, et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. J Allergy Clin Immunol. 2011;127:587–93. https://doi.org/10.1016/j.jaci.2011.01.038

A complete guideline written by the World Allergy Organization Anaphylaxis Committee.

23. Cheng A. Emergency treatment of anaphylaxis in infants and children. Canadian Paediatric Society Acute Care Committee. Paediatr Child Health. 2011;16:35–40.

24.• Dribin TE, Michelson KA, Monuteaux MC, Schnadower D, Neuman MI. Timing and predictors of repeat epinephrine administration among children hospitalized for anaphylaxis. J Allergy Clin Immunol Pract. 2019;S2213-2198(19):30854–2. https://doi.org/10.1016/j.jaip.2019.09.028

This article helps to make important clinical decisions, such as when to administer and repeat epinephrine in hospitalized children.

25. Niggemann B, Beyer K. Time for a new grading system for allergic reactions? Allergy. 2016;71:135–6. https://doi.org/10.1111/all.12765.

26.• Anagnostou K. Anaphylaxis in children: epidemiology, risk factors and management. Curr Pediatr Rev. 2018;14:180–6. https://doi.org/10.2174/1573396314666180507115115

In this article, risk factors for anaphylaxis are very well described, as well as anaphylaxis management in childhood.

Publisher's Note