Chapter

Anaphylaxis in Infants

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Abstract

Anaphylaxis is an extremely dangerous systemic hypersensitivity reaction that develops rapidly and can be fatal. Infants make up the most difficult group of patients with anaphylaxis, given the first episode of reaction occurring at an early age, there are age-related difficulties in interpreting complaints, unpredictability of clinical symptoms, prolonged process of diagnosis, and prescribing the appropriate treatment. These factors determine the risk of fatal outcomes, even in case of nearly healthy infants. For this group of patients, such problems as lack of available diagnostic tests, limited standard doses of epinephrine autoinjectors, the absence of predictors of occurrence, and severity of systemic allergic reactions are still relevant. This chapter presents the available information on the prevalence of anaphylaxis, the most common triggers, diagnosis, clinical symptoms, severity, and treatment in infants.

Keywords: anaphylaxis, anaphylactic reaction, trigger, allergen, children, food allergy, infants, molecular diagnostics, specific IgE, tryptase

1. Introduction

Anaphylaxis is an extremely dangerous systemic hypersensitivity reaction that develops rapidly and can be fatal [1]. More than 120 years have passed since the phenomenon of anaphylaxis was first described, but there are still numerous difficulties and questions related to the management of patients with this diagnosis. Physicians' attention to the problem of anaphylaxis has revived over the last 20–30 years, due to the increased prevalence of systemic reactions to various triggers (food allergens, medications, latex, physical exercise, etc.). Infants make up the most difficult group of patients with anaphylaxis, given the first episode of reaction occurring at an early age, there are age-related difficulties in interpreting complaints, unpredictability of clinical symptoms, prolonged process of diagnosis, and prescribing the appropriate treatment. These factors determine the risk of fatal outcomes, even in the case of nearly healthy infants. For this group of patients, such problems as lack of available diagnostic tests, limited standard doses of epinephrine (adrenaline) autoinjectors, the absence of predictors of occurrence, and severity of systemic allergic reactions are still relevant. This chapter presents the available information on prevalence of anaphylaxis, the most common triggers, diagnosis, clinical symptoms, severity, and treatment in infants.

2. Prevalence

Data on prevalence and incidence of anaphylaxis in infants are limited, and the younger the child, the less reliable information is available regarding the problem, but anaphylaxis occurs even in two-week-old infants [2–4]. Results of the epidemiological studies are variable, largely due to dissimilar methodologies; for example, analysis of referrals to allergy clinics or emergency departments will differ from the evaluation of the international anaphylaxis registry database or medical records review (epinephrine auto-injector prescription, epicrisis, and ICD code) or general survey of respondents. There are some features of the definitions used in various clinical and epidemiological studies in infants (0–36 months). The term "infants" is usually used for children during the first 2 years of life; in some studies, "infants" refer to children under the first 12 months of life (which is additionally reported); "toddlers" refer to children between 12 and 36 months of life; some researchers randomly select age periods (e.g., from 0 to 4 years).

According to numerous studies that analyzed medical documentation databases, the incidence of anaphylaxis in infants during the first 4 years of life was 3–4 times higher than in other age groups. In the city of Alcorcon (Spain), the peak incidence of anaphylaxis was found in children under 4 years old and amounted to 313.58 per 100,000 person-year between 2004 and 2005 [5]. The figures were three times higher than in older age groups. In Australia, there were reports about an increase in hospitalizations due to anaphylaxis from 4.1 to 19.7 per 100,000 person-year in children under 4 years old [6].

A number of studies report that anaphylaxis in infants ranges from 25% to 34% of all pediatric anaphylaxis cases, and the incidence is slightly higher in boys (56–69%) than in girls [7–11]. According to Huang et al. [12], the share of patients <1 year of life was 3.1% out of 192 children with anaphylaxis admitted to emergency department. According to our research conducted in Russia at the pediatric allergy department, more than half of patients (58%) with food-induced anaphylaxis had their first reaction episode between the age of 8 months and 2 years [13].

In recent years, there has been an increase in the prevalence of the disease in infants, especially food-induced anaphylaxis. Motosue et al. [14] reported a 129% increase in the number of admissions to emergency departments due to anaphylactic reactions in infants during the first 5 years of life between 2005 and 2014. In the state of Illinois (USA), there was a 29% annual increase in the number of referrals and admissions to intensive care units due to food-induced anaphylaxis in infants aged 0–4 years in 2008–2012 [15]. For instance, the incidence of food-induced anaphylaxis in this age group totaled 11.9 cases per 100,000 person-year in 2008 and increased to 30.5 cases per 100,000 person-year in 2012.

The foregoing data demonstrate the vulnerability of infants to increasing prevalence and risk of anaphylaxis. It is of paramount importance to consider that most of the data are underreported and cannot fully reflect the real epidemiological pattern, since many episodes of anaphylactic reactions in infants occur for the first time and some of them are overlooked.

3. Triggers

Food is the main trigger of anaphylaxis in infants. In older children, food-induced allergy causes at least 50% of all anaphylactic reactions, and in younger patients, it is up to 70–90% [7, 16, 17]. According to the study conducted in New Zealand, the retrospective

analysis of 10-year medical records of patients with ICD-9 code T78.0 (anaphylactic shock due to adverse food reaction) and T78.2 (anaphylactic shock unspecified) showed that incidence of food-induced anaphylaxis in patients under the age of 2 made up 50.5 per 100,000 person-year and significantly exceeded its rate in the total group of children (16.2 per 100,000 person-year) [18]. Colleagues in Singapore also demonstrated that the highest percentage of food-induced anaphylaxis cases occurs in infants under 2 years old (up to 90%), and the rate drops to 73% in children aged 2–11 [19].

Country	Authors	Study type	Number (N)	Age	Triggers		
					First place	Second place	Third place
Russia	Esakova et al., 2014 [13]	Retrospective analysis of medical records in tertiary hospital	N=46	0–2 years	Cow's milk (56,5%)	Hen's egg (15,2%)	Fish or/and seafood (13,1%)
China	Jiang et al., 2021 [17]	Retrospective analysis of medical records in tertiary hospital	N=134	0–2 years	Cow's milk (32,9%)	Hen's egg (21,4%)	Wheat (20,7%)
Korea	Jeon et al., 2019 [7]	Retrospective analysis of medical records in 23 secondary or tertiary hospitals	N=338	0–2 years	Cow's milk (43,8%)	Hen's egg (21,9%)	Walnut (8,3%)
France	Pouessel et al., 2020 [20]	Retrospective analysis of cases recorded by the allergy vigilance network	N=61	≤12 months	Cow's milk (59%)	Hen's egg (20%)	Wheat (7%)
USA	Rudders et al., 2011 [8]	Retrospective analysis of medical records in ED	N=61	0–2 years	Cow's milk (40%)	Peanut (31%)	Hen's egg (31%)
USA	Ko et al., 2020 [21]	Retrospective analysis of medical records in ED	N=448	≤12 months	Hen's egg (34%)	Peanut (22%)	Cow's milk (16%)
Turkey	Topal et al., 2017 [13]	Retrospective analysis of medical records in ED	N=23	≤12 months	Cow's milk (61%)	Hen's egg (21%)	Walnut (9%)
Turkey	Kahveci et al., 2020 [22]	Retrospective analysis of medical records in hospital	N=160	≤12 months	Cow's milk (51,4%)	Tree nuts (16,6%)	Hen's egg (15,4%)
Australia	Andrew et al., 2018 [23]	Retrospective analysis of medical records in EMS	N=127	≤12 months	Hen's egg (37,9%)	Tree nuts (31%)	Cow's milk (30,9%)
Spain	Alvarez-Perea et al., 2018 [24]	Retrospective analysis of medical records in ED	N=127	≤12 months	Cow's milk (67%)	Hen's egg (22%)	Fruits or fish (6%)

Table 1.
The most significant triggers of food anaphylaxis in infants.

Virtually any food can cause anaphylaxis in infants, but the most significant triggers in patients during the first years of life are cow's milk and hen's egg (**Table 1**). According to our data obtained in Russia, cow's milk (56.5%) and hen's egg (15.2%) were the most common allergens to cause food-induced anaphylaxis in infants <2 years of age [13]. It distinguishes them from older children because in this age group, tree nuts (29.4%), fish/seafood (26.5%), and fruit (23.5%) are the dominant triggers. Similar results are seen in studies from other countries. In the comparative study conducted in China, food allergens, such as cow's milk (32.9%), eggs (21.4%), and wheat (20.7%), were the most common triggers of anaphylaxis in infants <2 years of age, whereas in preschool (3–6 years) and school-aged children (7–12 years), fruits and vegetables (31.6% and 35.9%, respectively) were the major allergens [17]. In France, cow's milk (59%), hen's egg (20%), wheat (7%), and peanuts (3%) are the most frequent causes of anaphylaxis in infants <1 year of age [20]. According to Rudders et al. [8], cow's milk, peanuts, and hen's egg are the main triggers of anaphylactic reactions in infants <2 years of age in the United States, which is consistent with findings from another American study based on retrospective analysis of intensive care units' data covering the period between 2016 and 2018 [21]. Colleagues in Turkey also report that above 50% of food anaphylaxis cases in infants <1 year of age are associated with the consumption of cow's milk [11, 22]. In Australia, the most common trigger of anaphylaxis is hen's egg (39%) [23], in Spain, unlike in most countries, the top three allergens, along with cow's milk and eggs, include fruit and fish (9%) [24].

Sensitization to some allergens can occur at an early age when they are passed to a child in breast milk. So, anaphylaxis can occur both during breastfeeding (less common) and when the product is first consumed [25, 26]. Two cases of anaphylaxis in the form of urticaria, vomiting, cough, and wheeze have been described in exclusively breastfed infants during the first year of life and took place after the consumption of fish by the mother [26, 27]. Specific IgE to several types of fish was detected during the pediatric examination. In 1988, Lifschitz et al. [28] described a one-month-old patient with an anaphylactic reaction after consuming breast milk, which had been collected earlier before the child was found to be hypersensitive to cow's milk proteins; at that time, the mother was not following a dairy-free diet. In infants, anaphylactic reactions to various formulas, partially highly hydrolyzed, are possible [29]. Anaphylaxis can be induced by a high-hydrolysis formula not only in infants <1 year of age, a case of anaphylaxis after 3 years of milk elimination in a 5-year-old child during a provocation test with high-hydrolysis formula, sIgE level to cow's milk was 37.1 UA/mL (ImmunoCAP, Sweden) [30]. Cases of anaphylaxis after the first use of partial hydrolysate formula have been described in children who were previously exclusively breastfed with the exclusion of cow's milk protein by the mother [31].

Typically, cow's milk is the first foreign protein introduced into a child's diet, so it is one of the most frequent triggers of food anaphylaxis in infants. Pouessel et al. [20] reported that in 28 (46%) of 61 cases of anaphylaxis caused by cow's milk, the first episode of anaphylactic reaction was noted when this allergen was first consumed after cessation of breastfeeding. There are reports of anaphylaxis in infants with cow's milk allergy after the first consumption of goat's milk and soy-based formula [32]. Moreover, anaphylactic reactions in infants are possible even to less traditionally accepted products for this age: rare fruits and vegetables [33], seeds (pumpkin, sesame, and mustard) [34], different types of meat (e.g., caribou, whale) [35], bee products [36], etc.

One of the most difficult and unpredictable situations is anaphylaxis to hidden allergens, which sometimes are not mentioned in the product composition. Zurzolo

et al. [37] conducted a survey involving 198 respondents with food allergies, who retrospectively evaluated the development of anaphylaxis after consuming packaged food that did not contain the allergen in question. The share of such anaphylactic reactions amounted to 7%. Sometimes parents themselves do not properly read the labels, which leads to repeated episodes of anaphylaxis. For example, there was a case at our clinic, when a girl suffering from food allergy since an early age had an episode of anaphylaxis after the first consumption of peanut sticks at the age of 1.5. As for clinical symptoms, pronounced swelling of the neck, breathing difficulties, sweating, pallor, cyanosis, and repeated vomiting were noted. After the first episode of anaphylaxis, the child's parents tried to avoid food that might contain peanuts. But despite all efforts, 6 months later the child had another episode of anaphylactic reaction after eating bread, which contained trace amounts of peanuts, but the parents did not consider that. Such cases are far from isolated.

We should not forget the possibility of accidental non-oral contact of the child with the causative product. For example, inhalation of aerosolized food particles during cooking and skin contact with allergens. According to our observation, the rate of patients with anaphylactic reactions caused by skin contact or inhalation of allergen amounts to 16.4% [38]. The predominant triggers of anaphylaxis caused by skin contact are fish/seafood allergens (46%) and cow's milk (33%), and the most common triggers of anaphylaxis caused by inhalation are fish/seafood allergens (89%).

Anaphylactic reactions to drugs occur in a small percentage of cases in infants. The most common triggers of drug-induced anaphylaxis in children are antibacterial drugs, as per Xing et al. Ref. [39] analysis of 91 cases of drug-induced anaphylaxis in children showed that the share of reactions to antibiotics amounted to 53%. Topal et al. [11] described one patient with anaphylaxis to antibacterial drug in a group of children under one year of age. Nonsteroidal anti-inflammatory drugs are in second place in terms of incidence of anaphylaxis induction. Gabrielli et al. [40] showed that antibacterial drugs triggered 37.3% of drug-induced anaphylaxis in children (mean age 3.8 years old), while nonsteroidal anti-inflammatory drugs caused 21.6% of cases.

Various medications contain residual amounts of a food allergen and can cause anaphylaxis in infants. There is a report of an 11-month-old infant with atopic dermatitis and allergy to cow's milk proteins who had anaphylaxis episode 15 minutes after consuming bacilor (Lyocentre Laboratories, Aurillac, France) containing Lactobacillus rhamnosus [41]. Prick test with bacilor was positive.

Vaccination poses a threat of anaphylaxis in infants. Most vaccinations occur in the first two years of life, so there is no anamnestic data regarding tolerability and risk of adverse reactions. A population-based study reported an anaphylaxis rate of 1.31 cases per 100,000,000 doses for all age groups [42]. Vaccines contain not only immunogenic determinants but also trace amounts of various components that may be allergens. Therefore, sensitization, which can induce anaphylaxis by vaccination, may develop before the use of the vaccine or during the first and subsequent injections. The most significant inducers of anaphylaxis include hen's egg allergens, antimicrobial agents, and gelatin. For example, hen's egg protein is present in significant amounts (μg/ml) in yellow fever, influenza, varicella, rabies, measles, and mumps vaccines, and this amount may be sufficient to develop anaphylactic reactions in patients with anaphylaxis to hen's eggs [43]. Antimicrobial agents, neomycin, streptomycin, kanamycin, and polymyxin B may be present in trace amounts in live virus vaccines, so patients with a history of anaphylactic reaction to these antibacterial agents should not receive vaccines containing these components [44]. As a stabilizer, gelatin is contained in high concentrations in the yellow fever vaccine (up to 72 mg/0.5 ml dose) and in some

influenza vaccines (up to 250 mg/0.5 ml dose). Therefore, these vaccines may provoke anaphylaxis in patients highly sensitive to this component [45].

It is important that the presence of allergic diseases in the history of an infant is not necessarily a prerequisite for anaphylaxis. According to Pouessel et al. [20], 89% of children with food anaphylaxis in the first year of life had no previous food allergy; according to our observation, the proportion of such patients is up to 25% [13]. Among the cofactors that increase the risk of anaphylaxis in infants, Pouessel et al. [20] identified intake of proton pump inhibitor (esomeprazole) and acute respiratory infection at the time of anaphylactic reaction occurrence.

4. Clinical symptoms and diagnosis

4.1 Clinical criteria for diagnosis

In most cases, anaphylaxis in infants is typical and develops within a few seconds-minutes, usually within 2 hours after contact with the allergen, but regression of symptoms may develop gradually. Biphasic and protracted anaphylaxis are extremely rare in infants. The proportion of biphasic anaphylaxis is reported to be about 3–5% in infants with anaphylaxis <2 years of age [7]. There are isolated reports of biphasic anaphylaxis in infants. Lee et al. [46] described this form of anaphylaxis in two children aged 1 and 2 years. Pouessel et al. [20] described a case of the biphasic anaphylactic reaction of a 9-month-old child after consumption of a hen's egg; initially, there were symptoms in the form of vomiting, abdominal pain, and diffuse skin rash, which disappeared without any therapy, but 4 hours later the symptoms resumed and required epinephrine injection. Protracted anaphylaxis in infants is extremely rare. In our clinical practice, we observed an 8-month-old child with respiratory failure, angioedema, and generalized urticaria after the first consumption of three pine nuts. The child had repeated injections of epinephrine and artificial ventilation for 3 days.

To diagnose anaphylaxis, regardless of patient age, the 2005 clinical criteria of the Second National Institute of Allergy and Infectious Disease/Food Allergy and

Criteria	Characterization of symptoms [NIAID/FAAN, 2005]	Characterization of symptoms [WAOAG, 2020]
1	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) And at least one of the following: a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia); b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).	Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) And at least one of the following: a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia); b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence); c. Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens.

Criteria	Characterization of symptoms [NIAID/FAAN, 2005]	Characterization of symptoms [WAOAG, 2020]
2	Two or more of the following occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula); b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia); c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence); d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).	Acute onset of hypotension* or bronchospasm** or laryngeal involvement*** after exposure to a known or highly probable allergen**** for that patient (minutes to several hours), even in the absence of typical skin involvement.
3	Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*; b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.	
	PEF, Peak expiratory flow; BP, blood pressure. **Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg1[23age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.*	*PEF, Peak expiratory flow; BP, blood pressure.* **Hypotension is defined as a decrease in systolic BP greater than 30% from that person's baseline, or* *i. Infants and children under 10 years: systolic BP less than (70 mm Hgþ [2 x age in years])* *ii. Adults and children over 10 years: systolic BP less than<90 mmHg.* *** Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.* ****Laryngeal symptoms include stridor, vocal changes, and odynophagia.* *****An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (e.g., via direct activation of mast cells).*

Table 2.
Clinical criteria for diagnosis of anaphylaxis (anaphylaxis is highly likely when any one of the following criteria is fulfilled).

Anaphylaxis Network (NIAID/FAAN) [47] and the new 2020 clinical criteria of World Allergy Organization Anaphylaxis Guidance (WAOAG) [1] are used (**Table 2**). The distinctive feature of WAOAG criteria is the possibility of diagnosing anaphylaxis if an isolated potentially life-threatening bronchospasm or laryngeal involvement symptoms develop in response to allergen exposure. Such an approach helps to increase the verification rate of anaphylaxis diagnosis since isolated cases of acute

life-threatening allergic reactions deserve special attention according to most studies [48, 49]. According to our practice, the 2020 criteria are particularly relevant in pediatric or intensive care units providing emergency medical treatment.

Evaluation of anaphylaxis symptoms in infants in terms of existing criteria is often challenging, as it requires knowledge of the relevant nosology and clinical experience. In addition to the acknowledged symptoms of anaphylaxis, such as skin manifestations, problems with respiratory and cardiovascular system, gastrointestinal disorders, and behavioral reactions typical for infants are described by parents in many ways: "falling asleep," "goes limp," etc. Symptom descriptions can sometimes be influenced by national colloquialisms that are difficult for the physician to understand. For example, in Russia, parents sometimes describe their child's falling asleep with the term "to nod off," which is not at all associated with this symptom in other languages. Some children with anaphylaxis have rarer symptoms, such as hoarseness of voice, dysphonia, salivation, constant crying, and weeping. Studies covering the diagnosis of anaphylaxis in infants are sparse, but even based on the few data, some age-dependent features of the clinical pattern of anaphylaxis can be traced. It is highly likely that there is a connection between the trigger, shock organ involvement, and the severity of the reaction.

4.2 Clinical presentation and differential diagnosis of anaphylaxis in infants

Skin and mucous tissue manifestations are the most common for anaphylaxis in infants. According to most studies, the incidence of these anaphylaxis symptoms can be as high as 98–100% [11, 13]. This group of symptoms includes urticaria (usually generalized), erythema (more often multiforme), angioedema, and contact urticaria (infrequent, e.g., after contact with allergen). Retrospectively, photographs and questions to parents about skin manifestations are helpful: how quickly the rash appeared after exposure; how long the rash lasted; whether the rash was similar to the previous episodes; whether there was itching and other sensations; and where the rash was located. It is necessary to find out whether the child had a fever at the time the symptoms appeared, whether there were any other symptoms typical for infectious diseases, at what time of the day the rash appeared, etc. These questions will help to objectify clinical symptoms and rule out diseases not associated with systemic reactions (e.g., viral exanthem, mastocytosis, various forms of contact dermatitis).

Respiratory tract symptoms, along with skin manifestations of anaphylaxis in infants, more often rank second in incidence. However, in several studies, the incidence of respiratory symptoms of anaphylaxis in infants varies considerably and ranges from 48 to 98% [7, 8, 11, 17, 20, 21, 50]. Respiratory signs of anaphylactic reactions in infants include cough, stridor, wheeze, difficulties with inhalation and/or exhalation, rhinorrhea, and oropharyngeal symptoms (dysphonia, hoarseness/loss of voice, problems with swallowing). Several comparative studies demonstrated a significantly lower incidence of wheeze, cough, and dyspnea symptoms of anaphylaxis in infants compared with the older age group [7, 20, 22]. According to our data collected Russia, cough was observed in 73% of cases of food-induced anaphylaxis in infants [13]. However, cough associated with food intake can be due to many causes (e.g., introduction of complementary food of denser consistency, regurgitation, aspiration), which should be considered when evaluating this symptom in the diagnosis of anaphylaxis.

Gastrointestinal tract symptoms are particularly typical for the clinical picture of anaphylaxis in infants. As observed by Topal et al. [11], in children in the first year of life, the frequency of gastrointestinal symptoms in the form of persistent

vomiting reaches 30.4%, which, for example, is half as frequent (14.8%) in children over 1-year-old. Pouessel et al. [20] note that the rate of gastrointestinal anaphylaxis symptoms in infants <1 year of age is 49%, yielding only to skin and mucous membrane manifestations. According to the results of our investigation conducted in Russia among infants <1 year of age, in case of anaphylactic reactions after consumption of cow's milk, the frequency of gastrointestinal system involvement amounted to 53% and was many times higher, in comparison with the group of patients older than 1-year-old (11%) [51]. Such data emphasize the relevance of gastrointestinal symptoms as an important clinical criterion for the diagnosis of anaphylaxis in infants. However, the differential search should consider that vomiting and abdominal pain are quite common in infants and may be associated with refluxes, constipation, infections, acute surgical diseases, non-IgE-mediated allergic diseases, etc.

Cardiovascular symptoms in anaphylaxis are less common in infants. According to our observation and most studies, their incidence varies from 7 to 21% [8, 11, 20, 51]. One reason for the variability in the incidence of these symptoms is the frequent absence of blood pressure monitoring, and perhaps this examination is the most infrequent in such patients [52]. According to a study conducted at the pediatric emergency department in New York, only 12.5% of patients under 3 years of age had their blood pressure measured, compared with 90% of children above 3 years old [12, 53]. According to the study of Turkish colleagues, blood pressure in anaphylactic reactions was measured in only 21.7% of first-year infants, compared with 54.3% of patients older than 1 year of age [11]. The observed low incidence of cardiovascular anaphylaxis in this group of patients is often related to the lack of appropriate equipment, the necessary size of the tonometer cuff, and the difficulties with measuring blood pressure if the child is anxious. It should be emphasized that it is important not only to measure blood pressure once but also to monitor this indicator. In infants, hypotension is a late clinical sign indicating decreased tissue perfusion and decompensated shock, so it is crucial to diagnose anaphylaxis and start treatment, to recognize the earliest cardiovascular symptoms of shock: pallor, marbling, skin cyanosis, lethargy, hypotension, tachypnoea, increasing tachycardia (in the absence of crying) [54].

Thus, there are a number of circumstances that significantly complicate the diagnosis of anaphylaxis in the group of young children: the first episode of anaphylaxis, the presence of not clearly expressed and quickly disappearing symptoms, infants cannot describe symptoms and actively present complaints, so a number of subjective manifestations (itching, pain, sensations, etc.) cannot be assessed, the presence of nonspecific symptoms (crying, screaming, etc.) is extremely difficult to interpret, there are technical difficulties of objectification and monitoring. In this situation, the doctor's attention should be focused on finding out the contact with the suspected allergen, usually food in the case of infants.

Standardized criteria are used to assess the severity of anaphylactic reactions [55]. It is determined by the most affected organ system, but it is extremely difficult in the case of infants. Information about fatal anaphylaxis in the pediatric population is extremely limited and variable, and in general incidence does not exceed 1% [56]. Von Starck et al. [57] for the first time describe the fatal outcome of food-induced anaphylaxis of a boy aged 1.5 years. The child suffered from atopic eczema and had three episodes of generalized allergic reactions after eating several spoonfuls of mashed peas. After that, a provocation test with this product was carried out in the hospital, during which angioedema, cyanosis, and collapse developed. The boy died despite resuscitation. There are no reliable data on specific risk factors predisposing to fatal/almost fatal anaphylaxis in infants.

4.3 Laboratory diagnosis

Currently, there are no universal laboratory markers that can diagnose anaphylaxis with high probability, but some markers may be useful to confirm the diagnosis and determine the trigger. Practically applicable nonspecific tests include the determination of tryptase concentration in blood in the time interval from 15 minutes to 3 hours after the first symptoms of anaphylaxis and the dynamics after the anaphylaxis episode (basal tryptase level). It should be considered that the normal level of total tryptase among children <6–9 months of age is higher than among older children, adolescents, and adults. Thus, the average level of tryptase among children <3 months of age with hereditary predisposition to allergy is 14.2 ± 10.2 mg/l, while among healthy children it is 6.13 ± 3.47 mg/l [58]. With age, there is a gradual decrease in the level of tryptase, and only by 9–12 months of life, it reaches normal reference values (3.85 ± 1.8 mg/l), which can be objectively interpreted. Data from one study demonstrated elevated levels of β-tryptase in the blood of deceased patients diagnosed with sudden infant death syndrome (SIDS) [59]. Therefore, the authors suggest the possibility of undiagnosed anaphylaxis cases in infants disguised as SIDS. The results of another similar study were mixed [60]. Importantly, in the presence of an appropriate clinical pattern, low or normal tryptase levels do not exclude the diagnosis of anaphylaxis; this marker is most informative for drug, perioperative, and insect anaphylaxis and to a lesser extent for its other types.

To detect sensitization and to trigger anaphylaxis, the determination of specific IgE immunoglobulin using the ImmunoCap test system and the immuno solid-phase allergy chip (ISAC) is optimal in most cases, and these methods are highly informative. When performing allergy testing in infants, it should be borne in mind that even minimal detectable sensitization can be significant for the development of anaphylaxis. According to our observation, almost all patients with food-induced anaphylaxis, including infants, were able to detect sensitization to allergen; its level varied greatly (from threshold (≥0.35 kU/L) to maximum (>100 KU/L) (ImmunoCap, Phadia, Sweden) and did not correlate with the severity of reactions [13]. A certain degree of correlation was found only between specific IgE levels >100 KU/L to fish/seafood allergens and inhalation hypersensitivity inducing anaphylaxis by inhaling the allergen (e.g., cooking and cutting fish) [38, 61]. Jeon et al. [7] demonstrate that more than 90% of children with anaphylaxis to hen's egg <24 months of age and all children >2 years of age had sensitization to this allergen above DDP (95% decision points). However, specific IgE levels in cow's milk exceeded DDP only in less than half of the children with anaphylaxis to this allergen. Therefore, in case of negative allergy tests, but with a convincing history of anaphylaxis, it is necessary to repeat allergy testing over time. According to the research, the ISAC platform can be particularly useful in identifying triggers in patients with idiopathic anaphylaxis [62].

5. Treatment

Treatment of anaphylaxis in infants is completely based on the recommendations and principles of therapy of anaphylactic reactions in older patients (**Figure 1)** [58].

In case of anaphylaxis, treatment should begin immediately with a written protocol. It is necessary to stop receiving any suspected trigger (e.g., food and medication); evaluate blood circulation, skin, airway, breathing, age, and body weight; call the emergency medical service for help. Place the infant supine or semi reclining in a

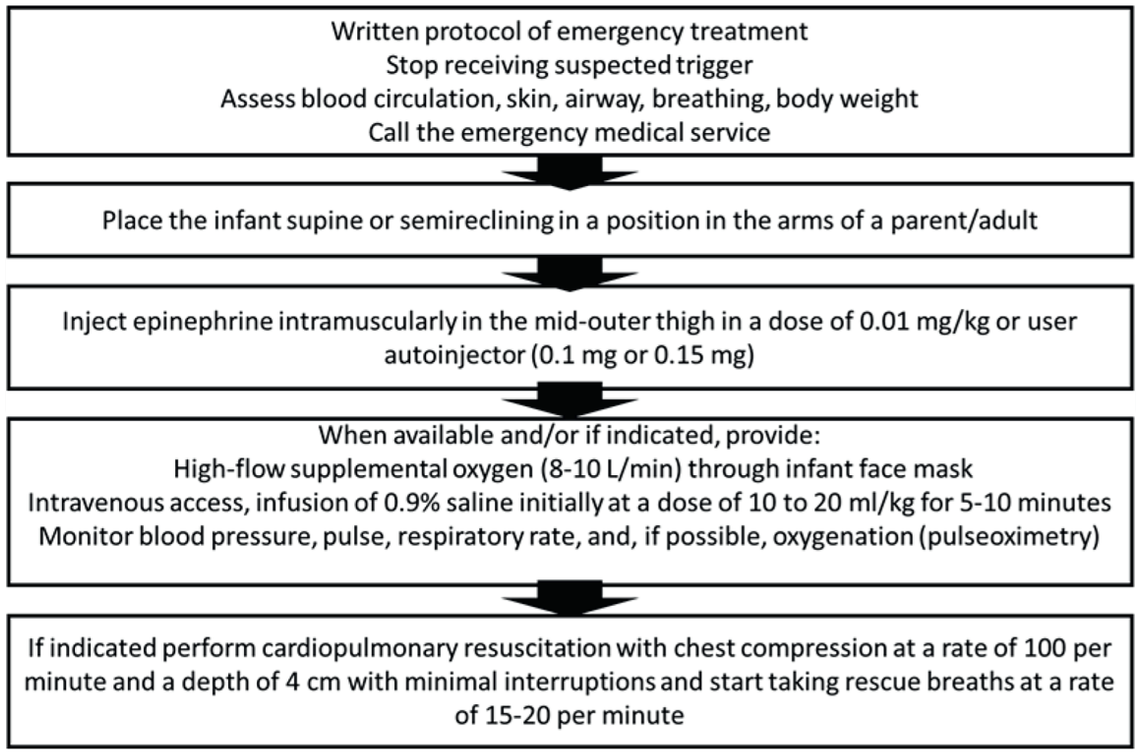

Figure 1.
Algorithm for the treatment of anaphylaxis in infants, data from Simons et al. [58].

position in the arms of a parent/adult (not upright over the shoulder) and immediately inject epinephrine intramuscularly in the mid-outer thigh. Anaphylaxis is an absolute indication for the administration of epinephrine (the first-choice drug), the recommended initial dose is 0.01 mg/kg intramuscularly. If there is no effect from the first dose, second administration is possible after 5–10 min. It is important that infants with anaphylaxis can remain pale despite 2–3 doses of epinephrine, so persistent pallor in itself is not a sign of poor treatment effectiveness and an indication for an increase in the dose of epinephrine, it should be interpreted taking into account blood pressure and other symptoms monitoring. In addition, more than 2–3 doses of epinephrine in infants can cause hypertension and tachycardia, tachycardia may be mistakenly interpreted as a continuing cardiovascular symptom of anaphylaxis [63]. When injecting epinephrine (especially when using an autoinjector) into an infant, it is necessary to fix the limb, this avoids traumatization and ensures the correct administration of epinephrine. After the injection of epinephrine, it is impossible to verticalize the patient's position (e.g., to sit down or get up), because this can lead to a fatal outcome within a few seconds. Most countries have registered autoinjectors for children weighing more than 15 kg in two fixed doses of epinephrine: 0.15 mg and 0.3 mg. Most infants weigh less than 10–15 kg; however, autoinjector containing the third dose of epinephrine - 0.1 mg was approved in November 2017 by Food and Drug Administration in the USA, but so far it is not available everywhere, which makes it difficult to administer the dose prescribed in the protocol for this category of patients. Using an epinephrine autoinjector with a dose of 0.15 mg for infants weighing 7.5 kg provides up to 200% of the recommended dose at a rate of 0.01 mg/kg [64, 65]. However, administering epinephrine *via* autoinjector presents less risk than using epinephrine syringes and ampoules, where dosing errors and delays in administration increase the potential risk, especially in the absence of medical

training. Another widely debated issue is the needle length of existing autoinjectors because it is not always suitable for intramuscular injection in infants. According to Kim et al. [66] who performed an ultrasound assessment of the distance from the surface to the thigh bone in 53 children (mean age 18.9 months, mean body weight 11 kg), it was found that using the existing autoinjector length of 12.7 mm (autoinjector 0.15 mg) in 43.1% of patients could lead to intraosseous infusion. Thus, there are quite significant difficulties for physicians when prescribing epinephrine to infants, which significantly reduces the frequency of its use. According to Fleischer et al. [67], only 29.9% of patients in the first 2 years of life use epinephrine to relieve symptoms of severe anaphylaxis. The researchers note that the reasons caregivers do not prescribe epinephrine are difficulty in recognizing the severity of anaphylaxis, lack of epinephrine, and problems associated with administering it. Similar findings were reported by colleagues in France, where only ¼ of patients under 1 year of age with food-induced anaphylaxis had injections of epinephrine, in none of these cases autoinjectors were used [20]. Research in Korea and Turkey demonstrated a higher rate of epinephrine administration in children under 12 months of age (46.8% and 40.6%, respectively) [7, 22]. According to our observation conducted in Russia, the frequency of prescribing epinephrine in infants to relieve symptoms of anaphylaxis 10 years ago did not exceed 7%; currently, there is a positive trend of higher incidence of prescribing epinephrine (21%) [13, 68].

Depending on the severity of the detected symptoms and the level of medical capabilities according to the indications additionally provided: high-flow oxygen supply through a facial infant mask (8–10 L /min); intravenous access and infusion of 0.9% saline initially at a dose of 10 to 20 ml/kg for 5–10 minutes. It is mandatory to monitor blood pressure, pulse, respiratory rate, and, if possible, oxygenation by using pulse oximetry. In the absence of a monitor to measure blood pressure, the pulse is counted manually every 2–5 minutes. You should be ready to perform cardiopulmonary resuscitation with chest compression at a rate of 100 per minute and a depth of 4 cm with minimal interruptions and start taking rescue breaths at a rate of 15–20 per minute [58].

The use of other adjuvant medications (H1-antihistamines, glucocorticosteroids, colloidal solutions, etc.) and additional therapeutic and diagnostic manipulations (oxygen support, measurement of blood pressure, resuscitation, etc.) to control the symptoms of anaphylaxis in infants is performed as per indications while respecting the advised doses of drugs, the algorithm of first aid in case of anaphylaxis in elderly patients. Although no adjuvant medication replaces epinephrine, antihistamines and glucocorticosteroids continue to be the predominant drugs by frequency of use in controlling the symptoms of anaphylaxis. Importantly, first-generation H1-antihistamines in common doses can cause sedation and conceal several symptoms, which may impede the diagnosis of anaphylaxis. In addition, their parenteral use can lead to a respiratory arrest in young children, as well as lower blood pressure, which justifies their use in anaphylaxis only when blood pressure is normal [69, 70].

In cases of anaphylaxis or suspected anaphylaxis in infants, admission to the intensive care unit and symptom monitoring for at least 24 hours is necessary. This recommendation is critically important for patients with severe or prolonged anaphylaxis (e.g., repeated doses of epinephrine or intravenous infusions are required), including in the anamnesis; if the patient has concomitant diseases (e.g., severe asthma, arrhythmia, mastocytosis); if the patient lives away from medical care; if anaphylaxis has developed in the evening or at night.

After a case of anaphylaxis, the patient should be prescribed epinephrine (autoinjector or syringe and ampoule) and clear recommendations should be given for its

administration. Moreover, currently, there are absolute and relative indications for prescribing self-injectable epinephrine in childhood, including children, who have not yet experienced anaphylaxis, but have a high risk of anaphylaxis, [71, 72]. **Table 3**. In our experience, among the absolutely presented indications for prescribing self-injectable epinephrine in infants, the most relevant are as follows: any history of anaphylaxis (including idiopathic anaphylaxis); food allergy and coexisting persistent asthma; previous cardiovascular or respiratory reaction to a food, especially in combination with gastrointestinal and skin/mucosal tissue symptoms. Among the relative presented indications for prescribing self-injectable epinephrine in infants, the most relevant are as follows: any reaction to small amounts of food (e.g., airborne food allergen or contact only *via* skin); history of only a previous mild reaction to peanut or a tree nut; high sensitization to specific food triggers known to be associated with severe/fatal reactions (e.g., peanut, tree nut, seafood, and milk); remoteness of home from medical facilities; certain comorbidities (asthma, mastocytosis). There are no absolute contraindications to administering epinephrine in children, because children usually do not suffer from any serious concomitant diseases, such as coronary heart disease or cardiac arrhythmias. If an infant with anaphylaxis has a high risk of tachyarrhythmias, the doctor should weigh the risks and benefits and take into account that epinephrine in anaphylaxis can save lives. Data from a number of studies [73–75] demonstrate that

Absolute indications [71]	**Relative indications** [71]
• Previous cardiovascular or respiratory reaction to a food, insect sting, or latex • Exercise-induced anaphylaxis • Idiopathic anaphylaxis • Child with food allergy and coexistent persistent asthma* **This is an opinion-based indication extrapolated from data emerging from retrospective studies.*	• Any reaction to small amounts of food (e.g., airborne food allergen or contact only via skin) • History of only a previous mild reaction to peanut or a tree nut • Remoteness of home from medical facilities • Food allergic reaction in a teenager
Examples of factors that may indicate the need to prescribe epinephrine for persons "at risk" of anaphylaxis [72]*	
Reaction history • Reaction to trace allergen exposure. • Repeat exposures likely. • Specific food triggers are known to be associated with severe/fatal reactions (e.g., peanut, tree nut, seafood, and milk). • Generalized urticaria from insect venom. **Certain comorbidities:** • Asthma • Use of nonselective β-blockers. **Additional factors:** • Initial reaction details unclear, possible anaphylaxis. • Those living in a remote area away from medical care/access. **An at-risk person can be, for example, one with a confirmed allergy to food or insect venom who has not experienced anaphylaxis. Note: the first episode of anaphylaxis can be fatal.*	

Table 3.
Indications for prescribing self-injectable epinephrine, data from Muraro A et al. [71], Sicherer S et al. [72].

up to 20% of patients with anaphylaxis need a second dose of epinephrine; in addition, one dose may not be enough to prevent the fatal outcome of anaphylaxis in some patients. In this regard, as a rule, the patient (the patient's parents) is recommended to have two epinephrine autoinjectors, this is due to a number of factors: the possibility of a misfire, remote residence from emergency medical care, a large body weight of the child (e.g., >45 kg), lack of effect from the first dose of epinephrine in the anamnesis, biphasic anaphylaxis, etc.

Allergy examination should be performed on all children with suspected anaphylaxis at allergy clinics with experience in the management of such patients. Information about anaphylaxis, and its causal factors (food, medication, insect sting, etc.) should always be available and accompany the patient, for example, indicated on a special medallion, bracelet, or clothing (e.g., t-shirts). Adults (parents, caregivers, teachers, etc.) surrounding the child with a history of anaphylactic reactions should be thoroughly informed about the diagnosis of anaphylaxis, the features of the clinical picture of its development, and a plan of emergency action, including mandatory administration of epinephrine. Particular attention should be paid to the exclusion of repeated episodes of anaphylaxis. In the group of infants <1 year of age, these reactions can be associated not only with misleading food labels and accidental contamination with allergen but also with deliberate attempts to expand the child's diet and introduction of previously excluded products to which children have been sensitized. Nowadays, there are training sessions on anaphylaxis (schools, online training, etc.) that help to significantly reduce anxiety in the family, because the presence of a child with this diagnosis provokes a state of fear for his life, due to the inability to provide timely treatment.

6. Conclusions

Thus, for young children, there are features of the triggers' spectrum and clinical manifestations of anaphylaxis, which should be considered when making a diagnosis, and to improve the existing clinical criteria of anaphylaxis in future. The development and availability of new types of autoinjectors for safe administration of epinephrine to small patients and the development of new therapeutic strategies for anaphylaxis are essential. The search for potential specific markers/predictors of anaphylaxis, applicable in routine practice to allow timely diagnosis of anaphylaxis and formation of a risk group before the development of a life-threatening situation, which is especially important for children in the first years of life, is relevant.

Conflict of interest

The authors declare no conflict of interest.

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