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Intensive Care for Anaphylaxis in Children: Current Trends

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ABSTRACT Anaphylaxis is an acute allergic reaction with rapid clinical development and risk of death. This article provides an analysis of literary sources devoted to intensive care of anaphylaxis in childhood. It was revealed that the prevalence of anaphylaxis is increasing, in children and adolescents as well. The main triggers of anaphylaxis in pediatric practice include food products, insect bites and drugs. Anaphylaxis is an IgE-mediated hypersensitivity reaction of type 1, characterized by the release of chemical mediators that lead to smooth muscle contraction, increased permeability and vasodilation and vagal activation. Clinically, anaphylaxis is manifested by allergic skin rash, angioedema, obstruction of the upper respiratory tract (URT), broncho-obstructive syndrome (BOS), arterial hypotension, tachycardia. Intensive care for anaphylaxis in children begins with stabilization of the condition: stopping the entry of a possible allergen into the body, hospitalization in the anesthesiology and intensive care unit, restoring patency of the URT, conducting oxygen therapy, monitoring vital functions. The first-line drug for the treatment of anaphylaxis in children is adrenaline at a dose of 0.01 mg/kg, which stops all the main pathophysiological links of anaphylaxis. Adrenaline autoinjectors are not used in the Russian Federation. Second-line drugs for intensive care for anaphylaxis in children include glucocorticosteroids (GCS), antihistamines, bronchodilators and infusion therapy. The effectiveness of GCS in anaphylaxis in children has not been proven, antihistamines can relieve skin manifestations of an allergic reaction, but do not affect vital disorders. Bronchodilators reduce BOS and are an additional treatment, while infusion therapy eliminates hypovolemia. Knowledge and timely implementation of modern care algorithms for anaphylaxis in children and adolescents will improve the quality of emergency care and reduce the risk of fatal outcomes in this pathology.

Keywords: anaphylaxis, children and adolescents, intensive care, adrenaline

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AAI — adrenaline auto-injector
ARF — acute respiratory failure
BOS — broncho-obstructive syndrome
BP — blood pressure
GCS — glucocorticosteroids
HES — hydroxyethyl starch
ICU — intensive care unit
IT — intensive therapy
NSAIDs — non-steroidal anti-inflammatory drugs
RCT — randomized clinical trial
URT — upper respiratory tract
WAO — World Allergy Organization

INTRODUCTION

Anaphylaxis is a severe and life-threatening allergic reaction in a child with rapid clinical evolution that requires timely intensive care in the intensive care unit (ICU) [1–5]. In 2020, the World Allergy Organization (WAO) updated its guidelines on anaphylaxis and introduced the following definition for this condition: "Anaphylaxis is a serious systemic hypersensitivity reaction characterized by potentially life-threatening respiratory and/or circulatory dysfunction affecting at least two organs, which may occur without typical cutaneous manifestations or hemodynamic shock" [6, 7].

Current studies report a significant increase in the incidence of anaphylaxis over the past 20 years, with children and adolescents being at increased risk of hospitalization in ICU [1, 5]. Data on the prevalence of anaphylaxis in children vary widely (from 8.4–111.2 per 100,000), as do mortality statistics for this condition (0.33–1.06 per 1,000,000) [7–10].

Most new cases of anaphylaxis are diagnosed in children under 4 years of age [3]. In children under 10 years of age, anaphylaxis occurs more often in boys than in girls [11], probably due to a higher incidence of food allergy in the former [9]. Overall, the highest diagnosis rate is for food anaphylaxis (1.4–76.7 per 100,000 with an estimated prevalence of 0.3 to 1.2%) [12].

Over the past decade, there have been significant advances in understanding the epidemiology, pathogenesis, and emergency care of anaphylaxis in children and adolescents [13]. These advances have led to improved therapeutic approaches for patients with anaphylaxis in pediatric practice [13]. However, anaphylaxis remains underdiagnosed and there are challenges in providing emergency care for this pathological condition, primarily including the underuse of epinephrine as first-line therapy, as well as the overuse of antihistamines and glucocorticosteroids (GCS) at this stage of emergency care for children [13, 14].

In addition, anaphylaxis in young children often poses a particular challenge, as the broad spectrum of clinical manifestations and children's inability to describe their symptoms may hinder rapid diagnosis and emergency care [15]. Misdiagnosis and delayed IT of anaphylaxis in children and adolescents can lead to fatal outcomes [4, 7, 15]. In addition, there are significant differences between some emergency care algorithms regarding the use of treatments for anaphylaxis, which confirms the need for future studies to evaluate the effectiveness of drugs in IC for the recovery from this pathological condition [16].

The aim of this review was to highlight issues primarily related to the characteristics of IT for anaphylaxis at the present stage.

TRIGGERS AND PATHOGENESIS OF ANAPHYLAXIS

The most common potential allergic triggers causing anaphylaxis in children and adolescents include: foods (33%), insect bites (19%), and drugs (14%) [4, 17–19]. The most common food triggers include peanuts and cow's milk, which are more common in the pediatric population [3, 15, 20]. Less common causes include: anaphylactic reactions to animals (cats), latex, cleaning products, and environmental allergens [3, 17]. Less common triggers also include drugs: antibiotics (β-lactam antibacterial drugs, penicillins, cephalosporins), antipyretics, muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), and topical agents (medicinal ointments and gels) [10, 21]. In approximately 25% of cases of anaphylaxis in children, the trigger remains unknown [17].

It has been shown that the type of anaphylaxis triggers in children changes with age [3]. Food products are the most common allergens in children under 6 years of age, with milk and chicken egg white predominating in children under 2 years of age [3]. Anaphylactic reactions to hazelnuts and cashews are typical for preschoolers, and peanuts cause anaphylaxis in children of any age [3]. Insect venoms (wasps, bees) are the main cause of anaphylaxis in school-age children and adolescents, while drugs cause anaphylaxis mainly only in adolescents [3, 18]. Concomitant chronic diseases such as acute stenosing laryngotracheitis, bronchial asthma and atopic dermatitis increase the risk of severe anaphylaxis in childhood [22].

Anaphylaxis is typically an IgE mediated hypersensitivity reaction (type 1) characterized by the release of numerous chemical mediators following degranulation of basophils and mast cells (following repeated exposure to a specific antigen) [23, 24]. These chemical mediators include histamine, tryptase, carboxypeptidase A, and proteoglycans [24]. By activating phospholipase A, cyclooxygenases, and lipoxygenases, they form arachidonic acid metabolites including leukotrienes, prostaglandins, and platelet-activating factors [25]. The inflammatory response in anaphylaxis is primarily mediated by TNF-alpha (tumor necrosis factor) [24].

The pathophysiological effects caused by the release of mediators (histamine, leukotrienes and prostaglandins) are manifested by contraction of smooth muscles, increased permeability and vasodilation, as well as stimulation of the nervous system with reflex activation of the vagus [23].

MAIN CLINICAL MANIFESTATIONS

Anaphylaxis has several main clinical manifestations, such as skin rash (usually urticaria), angioedema, respiratory symptoms (obstruction of the upper airway, biofeedback), gastrointestinal (abdominal pain, diarrhea) and cardiovascular symptoms (hypotension, tachycardia, syncope) [3, 4, 26, 27]. The skin is the most frequently affected organ, but in about 10% of children and adolescents with anaphylaxis, skin symptoms may be absent, which can lead to an erroneous diagnosis [15].

Today, anaphylaxis is understood to have two clinical variants [3, 9, 19, 27, 28]:

1) any acute disease with typical skin manifestations (urticarial rash or erythema and/or angioedema) in combination with damage to the respiratory system and/or cardiovascular system and/or persistent severe gastrointestinal symptoms; or

2) any acute onset of arterial hypotension, BOS or airway obstruction, even in the absence of typical skin reactions.

Anaphylaxis often results in anaphylactic shock, an acute circulatory failure characterized by a decrease in systolic blood pressure (BP) below 90 mm Hg or by 30% of the working level, leading to hypoxia of vital organs [10]. Arterial hypotension is a late manifestation of decreased tissue perfusion and indicates decompensated hemodynamic shock [29]. Arterial hypotension is preceded by signs of compensated hemodynamic shock, including tachycardia, cold and pale extremities, cyanosis, impaired level of consciousness, and tachypnea [29].

Characteristic clinical symptoms of anaphylaxis develop within minutes to hours after exposure to a potential trigger [3]. In children and adolescents, anaphylactic reactions may be: 1) monophasic (occurring immediately after exposure to the allergen and resolving with or without treatment within minutes to hours); 2) biphasic (recurring after the initial symptoms have resolved, usually about 8 hours after the first onset of the reaction); or 3) prolonged (persisting for hours to days after the initial reaction) [17].

INTENSIVE CARE OF ANAPHYLAXIS IN CHILDHOOD

General aspects

When acute clinical signs of anaphylaxis appear, the first step is to remove any suspected trigger that could potentially cause an anaphylactic reaction [19, 30]. In some situations (e.g. intravenous infusion of a possible allergen drug) this can be done quite quickly [30]. Application of a tourniquet and/or subcutaneous injection of epinephrine around a local

allergen depot (e.g. a wasp sting or an antibiotic injection site) is no longer recommended due to limited therapeutic benefit and the risk of losing time for more important therapeutic measures [30]. If removal of the allergen is time-consuming (gastric lavage), it should not be done [10].

Next, the child's airway patency, adequacy of breathing, blood circulation, and skin condition should be assessed [19]. The child should be in a supine or semi-recumbent position in the arms of a health worker [19]. If hemodynamics are impaired, it is necessary to consider the child's position with the lower limbs elevated for effective cardiac output [3]. The vertical position during anaphylaxis is highly undesirable, as it is associated with an increased risk of death due to the "empty right ventricle" syndrome [31].

The child should be connected to a cardiac monitor to determine the respiratory rate, heart rate, oxygen saturation level (SpO_2) and blood pressure [21]. In case of severe manifestations of URT obstruction, the appearance of signs of acute respiratory failure (ARF), immediate administration of humidified 100% oxygen through an oxygen mask or intranasal cannula with a high flow rate (8–10 l/m) is recommended [10, 19, 30]. In some cases, the installation of a laryngeal mask may be useful, and in rare clinical situations (with a dramatic increase in ARF and the occurrence of apnea), there may be a need for endotracheal intubation followed by transfer of the child to artificial ventilation [30].

PHARMACOLOGICAL CORRECTION OF ANAPHYLAXIS

First line drugs (adrenaline)

Adrenaline (epinephrine) is the only effective first-line drug for IT anaphylaxis, which is supported by epidemiological data, animal studies, data on the mechanism of action and consensus opinions based on long-term clinical experience [22, 32, 33]. A recent European systematic review of the literature, consisting of 50 studies, which included a total of 18,449 participants, confirmed that adrenaline is the only pharmacological drug that affects the pathophysiological links of anaphylaxis, including in pediatric practice [34].

Its prompt and timely administration is critical for adequate treatment of severe anaphylactic symptoms and prevention of a biphasic reaction [35]. Delayed administration of epinephrine (or no administration at all) is associated with increased mortality and a higher risk of fatal anaphylaxis [7, 32].

However, despite the existence of national and international guidelines and awareness campaigns on anaphylaxis, epinephrine remains underused in emergency care and AP and GCS are overused as first-line therapy [7].

Adrenaline has a pronounced α- and β-sympathomimetic effect [9, 28]. α-1-adrenergic effect is manifested in increased vasoconstriction, increased peripheral vascular resistance and decreased edema of the upper respiratory tract mucosa [28]. β-1-adrenergic effect leads to increased inotropic and chronotropic effects, and β– 2-adrenergic effect leads to increased bronchodilation [17, 19, 27, 32]. It is important to note that this is the only drug that inhibits further release of inflammatory mediators from mast cells and basophils during anaphylaxis (i.e. suppresses the activity of inflammatory mediators) [9, 19, 28].

Thus, by activating α- and β- adrenergic receptors, adrenaline functionally counteracts all important pathophysiological links of anaphylaxis by reducing vasoconstriction, decreasing vascular permeability, bronchodilation, reducing edema and having a positive inotropic effect on the heart [17, 19, 27, 30].

Given the rapid onset of anaphylaxis, its potential severity and ethical concerns, there are currently no published studies on the pharmacodynamic dose-response of epinephrine in anaphylaxis, including in children and adolescents [27]. Epinephrine dosing is mainly based on common practice and limited studies in healthy volunteers [36, 37].

The recommended single dose of adrenaline in pediatric practice for anaphylaxis is 0.01 mg/kg [3, 10, 17, 19, 38]. The initial dose for intramuscular administration recommended for children weighing

up to 30 kg (0.01 mg/kg or 0.1–0.3 mg) is comparable to the doses used for resuscitation in asystole [37]. The maximum single dose for stopping anaphylaxis for children aged 6–12 years is 0.3 mg, and for children under 6 years — 0.15 mg [10].

An undiluted 1:1000 solution (1 mg/ml) of adrenaline is administered intramuscularly into the anterolateral thigh (this localization is preferable compared to administration into the deltoid muscle) [3, 10, 17, 32]. Adrenaline administered intramuscularly into the outer part of the middle thigh is quite safe and begins to act within a few minutes [28]. There are no contraindications to intramuscular administration of adrenaline in the treatment of anaphylaxis in children [22]. It is recommended to administer adrenaline intramuscularly rather than subcutaneously, since the former option leads to a higher peak concentration in plasma (2136±351 versus 1802±214 pg/ml) and a more rapid onset of action (8±2 pg/ml versus 34±14 min) [3]. Therefore, subcutaneous injections of adrenaline are not recommended due to insufficient absorption, resulting in a delayed onset of action, and should therefore be avoided [27, 30]. Intravenous bolus administration of adrenaline is associated with a significantly increased risk of side effects (arrhythmia) and overdose, and is therefore used only in extreme cases [32, 39]. For example, if a child is undergoing resuscitation (respiratory and/or circulatory arrest), adrenaline should be administered intravenously [30]. For this purpose, a dilution of 1 mg of adrenaline in 10 ml of physiological sodium chloride solution is administered, i.e. a solution with an adrenaline content of 0.1 mg/ml, under constant monitoring of circulatory parameters [30].

In case of absence of clinical response (in the presence of ongoing symptoms), intramuscular injections of epinephrine are repeated every 5–10 minutes after the first dose [3, 10, 27, 30]. Repeated administration of epinephrine is also recommended in case of suboptimal clinical response or progression of anaphylactic symptoms [17]. Administration of other drugs such as antipsychotics or corticosteroids should not delay the administration of epinephrine, as they are not the drugs of choice in the first-line treatment of anaphylaxis [9, 28].

If 3 boluses of adrenaline administered intramuscularly are ineffective for managing anaphylaxis, it is recommended to start an intravenous infusion at a dose of 0.1 mcg/kg/min with titration of the dose (up to 1 mcg/kg/min) [10, 17, 27, 30].

After the administration of adrenaline in children, side effects such as pallor, tremor, anxiety, dizziness and headache may be observed [17, 27]. Persistent pallor of the skin in itself is not an indication for increasing the dose of adrenaline [27]. In addition, the administration of more than 2–3 doses of adrenaline in children can cause hypertension and tachycardia, with tachycardia often being mistakenly interpreted as ongoing cardiovascular decompensation [27, 39].

Additional inhalations of adrenaline after intramuscular administration are effective in cases of laryngeal edema, as well as in BOS [30]. For this purpose, it is recommended to administer adrenaline (e.g. 2 ml at a concentration of 1 mg/ml) together with oxygen via a nebulizer and face mask or intranasal cannulas [30]. It should be remembered that the use of inhaled adrenaline cannot replace its parenteral administration [30].

Adrenaline autoinjectors (AAIs) allow rapid and reliable intramuscular administration of adrenaline [27]. They were developed and introduced into practice since 1987 to facilitate the administration of adrenaline in emergency situations by non-medical people [17, 27, 37]. AAIs also reduce the risk of dosing errors associated with the use of ampoules and syringes containing adrenaline, especially in public places [36].

To date, these devices have not been registered in the Russian Federation [37]. There are a number of limitations in the use of AIA: their availability, cost, lack of the possibility of individually selected dosage, limited shelf life (up to 18 months) [37].

The dosage of adrenaline using the AIA is 0.15 mg for children weighing 10–25 kg and 0.3 mg for children weighing more than 25 kg [17, 19]. If the first injection via the AIA is ineffective, the second dose can be administered after 5–10 minutes, depending on the patient's condition [17].

Second line drugs

Agents that can be used as adjunctive therapy to epinephrine in the treatment of anaphylaxis include corticosteroids and anticoagulants (H_1 and H_2), bronchodilators, and infusion solutions [30]. None of these drugs should be used as initial or sole treatment, as they do not relieve upper airway or lower airway obstruction, arterial hypotension, or reduce the likelihood of death in children with anaphylaxis [30].

Glucocorticosteroids

Historically, corticosteroids have been used to prevent prolonged and biphasic anaphylaxis reactions [28]. Today, corticosteroids are not recommended as a routine method for the treatment of anaphylaxis in children and adolescents and can be considered only as second-line drugs [3, 40]. It has been shown that due to the slow onset of action, corticosteroids play a very minor role in the acute phase of anaphylaxis treatment [30]. A large prospective analysis showed that prehospital administration of corticosteroids in children with anaphylaxis was associated with an increased rate of hospitalizations to the ER [41]. Okubo et al. showed that the use of corticosteroids in children and adolescents with anaphylaxis did not reduce the rate of relapses and increased the length of hospital stay [42]. A meta-analysis that assessed the studies on the use of corticosteroids in children with anaphylaxis from 1982 to 2011 did not find any randomized clinical trials (RCTs) on this issue [43]. A recent systematic review and meta-analysis that included 27 studies with 4114 cases of anaphylaxis, of which 192 (4.7%) had biphasic reactions, demonstrated that the use of corticosteroids did not affect the likelihood of developing a late-phase reaction [44]. Other studies have also failed to demonstrate their ability to prevent biphasic reactions [3, 45]. A 2020 systematic review also found no evidence of this effect [35]. In fact, recent data have shown that systemic corticosteroids for anaphylaxis may even increase the risk of a biphasic reaction in children with anaphylaxis [35].

Thus, the benefit of GCS in anaphylaxis has not been proven, but they are sometimes prescribed after the administration of adrenaline in children with a history of reactive airway disease [27]. To date, the use of GCS can only be justified in children with anaphylaxis who have clinical manifestations of BOS [46].

Antihistamines

Histamine is only one of many inflammatory mediators released during anaphylaxis [28]. Therefore, antihistamines in children are only justified as second-line agents for the relief of symptoms of urticaria and pruritus; they do not treat or prevent anaphylaxis or biphasic reactions [3, 27, 40]. Antihistamines have not been shown to improve respiratory or cardiovascular outcomes or improve survival in pediatric anaphylaxis [28, 40, 47]. Systematic reviews of the literature have not identified any RCTs supporting the use of antihistamines in childhood anaphylaxis [47, 48].

Currently, in international guidelines, are even classified as third-line therapy; their use is limited to the relief of skin symptoms and should in no case delay the administration of adrenaline or infusion therapy during stabilization of the patient's condition [3, 9, 27, 28].

Although antihistamines are not recommended for the initial treatment of anaphylaxis, their use may help in the treatment of cutaneous symptoms (such as urticaria or angioedema) [10, 49]. Non-sedating antihistamines (eg, cetirizine) are preferred because first-generation antihistamines (such as chlorphenamine) may cause sedation and may cause hypotension when given as a rapid intravenous bolus [28, 40].

Bronchodilators

Bronchodilators, such as inhaled β- adrenergic agonists (salbutamol), are recommended for BOS after the administration of adrenaline, in a quantity

of 2–4 inhalations [27, 30]. Bronchodilators are an additional treatment, since they do not prevent or alleviate the swelling of the URT mucosa, which is managed by α-1-adrenergic effects of adrenaline [30, 35].

Infusion therapy

An important pathophysiological aspect of anaphylaxis is the resulting hypovolemia, which is relieved by adequate fluid replenishment [30, 35, 36]. In severe anaphylactic reactions, large amounts of fluid must be administered over a short period of time [30].

Children should receive saline solution in boluses of 20 ml/kg each over 5–10 minutes, which can be repeated if necessary [3, 10]. Larger volumes of fluid may be required thereafter: up to a maximum of 1 liter over the first 30 minutes (subsequent dose is calculated based on the child's weight at 100 ml/kg) [19, 27, 50].

When conducting infusion therapy for anaphylactic reactions, crystalloid solutions should be used first: 0.9% sodium chloride solution or balanced electrolyte solutions [10, 30]. It should be remembered that when large amounts of electrolyte solutions are administered, they remain in the intravascular space only for a short time [30]. Glucose solutions are not recommended for anaphylaxis in children due to rapid extravasation of the administered volume [10].

In the absence of stabilization after the use of large volumes of electrolytes (up to 100 ml/kg), the possibility of additional use of colloidal solutions can be considered [30]. Gelatin and dextran solutions, despite their positive properties, should be considered with caution in children due to their ability to release histamine and the possibility of causing anaphylaxis [30]. Hydroxyethyl starch (HES) preparations, such as medium molecular weight HES (6%), at a dose of 10 ml/kg are the most commonly used volume substitutes in anaphylactic shock in children and adolescents [30].

CONCLUSION

Anaphylaxis in children is a severe, potentially life-threatening systemic allergic reaction that requires urgent clinical care. Timely evaluation and treatment are essential, as delays in treatment are associated with an increased risk of death. Anaphylaxis is primarily a clinical diagnosis: healthcare providers should be trained to recognize and administer intramuscular epinephrine as part of a comprehensive treatment plan. Epinephrine is an underused first-line treatment for anaphylaxis. Better understanding and knowledge of emergency management algorithms for anaphylaxis in pediatric patients should improve the quality of care.

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