



Drug-Induced Anaphylaxis in Children

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Abstract

Purpose of review To describe and analyze epidemiology, major triggers, diagnosis, and management of drug-induced anaphylaxis in pediatric population.

Recent findings Despite the fact that foods are the most common elicitors of anaphylaxis during childhood, frequency of those reactions during adolescence seems to be increasing and they are associated with more severe reactions. Betactam antibiotics and non-steroidal anti-inflammatory drugs are described as major triggers of those reactions. Despite its higher severity, anaphylaxis continues to be underrecognized and undertreated.

Summary Drugs are associated with more severe anaphylactic reactions in all age groups, but it is still underdiagnosed and wrongly managed. Patients who seek assistance for anaphylaxis in the emergency departments should be referred to an allergist consultation and pediatricians should be better trained to recognize and correctly manage this severe condition.

Introduction

Anaphylaxis is defined as a severe, life-threatening generalized or systemic immediate-type hypersensitivity reaction. Anaphylaxis in children and adolescents is a

potentially life-threatening condition. Anaphylaxis occurs in patients of all ages, but research and most guidelines are focused on adults. Little is known about the

occurrence of severe allergic reactions on a population level and even less is known for pediatric anaphylaxis [1•, 2].

Foods are the most common triggers of severe allergic reactions in childhood, followed by drugs, latex, and insect venoms [3••]. Drugs become more important elicitors of anaphylaxis from adolescence [4]. Hospital admissions for anaphylaxis seem to be increasing in many countries, particularly in children and patients with food allergy (FA). On the

other hand, in adults, drugs are associated with more severe anaphylaxis, including fatal anaphylaxis [3••, 5].

As drugs are associated with more severe immediate hypersensitivity reactions and are among the most common elicitors of anaphylaxis in the pediatric population, this review will focus on those triggers, analyzing the epidemiology, clinical diagnosis, and the risks associated with underdiagnosis and wrong management.

Epidemiology

Anaphylaxis is the most severe form of an allergic reaction. Population studies have estimated the incidence or prevalence of anaphylaxis in western countries to be in the range of 8–50 per 100,000 person/years [6, 7]. However, robust data regarding anaphylaxis epidemiology in the pediatric population is still missing.

In studies assessing anaphylaxis in children, triggers seem to vary between different ages and different countries. The European Anaphylaxis Registry reported that food was the most important trigger, but the frequency was highly variable according to age, ranging from 88% in preschoolers to 54% in adolescents. On the other hand, drug-induced anaphylaxis increased from 13 to 22% between those ages [4]. In Australia, food responded to 85% of pediatric anaphylaxis, while drugs were responsible for 6% [8].

In Latin America, a multi-centric case series of pediatric anaphylaxis was published a few years ago. It was demonstrated that in children older than 6 years of age, drugs (mostly non-steroidal anti-inflammatory drugs and antibiotics) were the main triggering agents [9•]. Although triggers may vary between different parts of the world, we must point out that anaphylaxis in Latin America has been documented in registries almost exclusively by allergists. We believe that, at least in Brazil, the majority of patients presenting food-induced anaphylactic reactions are seen by pediatricians and are not referred to allergists, which can explain many underreported cases of anaphylaxis induced by food.

When studies evaluated the relationship between anaphylaxis severity and other factors, such as gender or triggers, results also differ. Liew et al. performed an interesting study in Australia, assessing data about fatal anaphylaxis from 1997 to 2005. They found no difference between genders for fatalities caused by drugs. Moreover, they described that fatal drug-induced anaphylaxis was more common in adults and its incidence was increasing [10, 11].

In a large case series in the USA, it was also reported that fatal anaphylactic reactions were induced by drugs in 58.8% of 2458 patients. However, only 3.4% of those fatalities related to drug exposure occurred in children or adolescents [12]. Then, we can conclude that fatal anaphylaxis induced by drugs is a rare condition in children, but data from different populations are required.

It has been postulated that hospital admissions due to anaphylaxis are increasing, mainly because of food-induced anaphylaxis, and fatalities have

already increased, due to reactions induced by drugs [5, 13•]. Moreover, recent data from Australia report an increase in hospitalization rates due to all causes of anaphylaxis, both in children under 4 years and in those between 5 and 14 years of age, between 1998 and 1999 and 2011–2012. Thus, when data was evaluated according to the eliciting agent, drug-induced anaphylaxis admissions were fourfold higher in 5–14 years of age children [14••].

There are few data about intensive care unit admissions due to anaphylaxis in children. A recently published study in France evaluated 166 pediatric admissions in ICU because of anaphylactic reactions, between 2003 and 2013. It was described that drug-induced anaphylaxis was responsible for 50% of those admissions, while food reactions were cited in 37% of these cases, showing that, despite being less frequent, reactions induced by medications are associated with higher severity [3••].

Finally, the frequency of drug groups involved in anaphylactic reactions also varies between age groups and countries. In children, analgesics and antibiotics are the main triggers of drug-induced severe immediate reactions. In most epidemiologic studies, betalactam (BL) antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly reported [4, 15–17].

However, there must be differences in terms of genetics and exposition to different classes of drugs. In a recently published case series from China, there was no NSAID-induced anaphylaxis among 91 children with anaphylactic reactions induced by drugs [18]. On the other hand, in Brazil, NSAIDs are the major triggers in adults and children [19•, 20].

Mechanisms involved and cross-reactivity/intolerance

Anaphylaxis is a serious, life-threatening and immediate systemic hypersensitivity reaction mediated by mast cell and basophil degranulation, usually occurring during the first hour after drug administration. Clinical presentation ranges from isolated skin signs and symptoms, such as urticaria or angioedema, until systemic reactions, as anaphylaxis. Anaphylaxis can be allergic, usually IgE-mediated, or non-allergic, being BLs and NSAIDs the main inducers of these reactions [18].

Penicillins and Cephalosporins share a common BL ring attached to a 5-membered thiazolidine ring with a side chain (R1) or a 6-membered sulfur-containing dihydrothiazine (cephem) ring with 2 side chains (R1 and R2), respectively [21, 22]. The BL ring, the thiazolidine/dihydrothiazine rings, and the side chains are all potentially immunogenic. It was previously considered that cross-reactivity between BL antibiotics was frequent and it would be induced by immunologic responses to BL ring or even the thiazolidine/dihydrothiazine rings. However, recent data suggest that cross-reactivity between cephalosporins and penicillin occur in less than 1–2% of all cases and is mostly induced by immunologic recognition of the side chains (R1 and R2) [23, 24]. Then, it is crucial to investigate patients with previous suspected BL hypersensitivity reactions in order to confirm it and to define possible tolerance to other BL antibiotics.

Many studies performed in the last 10 years evaluated reactions to cephalosporins [25•]. In Italy, ceftriaxone is the most frequently prescribed cephalosporin for intravenous or intramuscular administration, and it is responsible for

the highest number of severe adverse reactions in children [21]. Mori et al. studied 1264 children with history of BL allergy, 7.1% induced by ceftriaxone. When the reactions were IgE-mediated, most individuals could tolerate amoxicillin, suggesting that in patients with mild reactions to ceftriaxone, pediatricians should be more confident when prescribing oral amoxicillin [21].

Several non-immune-mediated mechanisms of anaphylaxis have been described, such as direct degranulation of mast cells/basophils, complement activation, adenosine, cyclooxygenase metabolism interferences, and contact system activation. Particularly in hypersensitivity reactions to NSAIDs, non-allergic reactions are more frequent than IgE-mediated reactions, and are responsible for those induced by more than one group of NSAIDs ("cross-intolerant" patients) [19•, 26].

Risk factors

Studies about risk factors of anaphylaxis are conflicting. Vatander et al. did not find any association between the risk of allergic reactions to drugs and history of asthma or eczema [27•]. In contrast, O'Keefe et al. reported that the risk of anaphylaxis was higher in patients with asthma [28].

In a recent manuscript published by Bernhardt Sachs et al., authors evaluated possible drug-induced anaphylaxis cases in a pediatric population [14••]. After defining "validated cases," they concluded that risk factors for their occurrence were heterogeneous, depending on the involved drug. More severe reactions were associated with atracurium administration, whereas analgesics induced more urticaria, for example. Moreover, atopy was considered a risk factor for antibiotic-induced reactions. Finally, 3.8% of all patients had previously reacted to the eliciting drug, showing that a detailed clinical history could prevent many severe reactions [15].

Recurrent reactions occur most commonly with foods than drugs, and normally with the same trigger of the index reaction [3••]. There was no association between reaction recurrence and gender, age, severity of the index anaphylactic reaction, or duration of follow-up [3••].

Clinical presentation and diagnosis of anaphylactic reactions

The clinical presentation of anaphylaxis is heterogeneous. The following symptoms may occur similarly in all ages: urticaria, pruritus, erythema/flushing, angioedema, abdominal pain, diarrhea, bronchospasm, loss of consciousness, shock, and life-threatening respiratory or cardiac arrest. Most reactions are mild and only rarely progress into severe anaphylaxis [3••]. Dyspnea is the leading reported symptom (35.8%), considering all validated cases, whereas urticaria (40.0%) ranked first in analgesic-/antipyretic-induced cases [29].

The diagnosis of anaphylaxis depends on recognition of characteristic symptoms and signs that occur minutes to few hours after exposure to a known or potential trigger (Table 1) [1•]. The National Institute of Allergy and Infectious Diseases Guidelines defined clinical criteria for anaphylaxis diagnosis [1•, 30, 31]. Therefore, the diagnosis of anaphylaxis is based on clinical findings observed during the reaction, although the measurement of biomarkers, such as tryptase or histamine, can help in confirming it [32•, 33].

Table 1. Clinical criteria for the diagnosis of anaphylaxis (adapted from Simon FE et al.) [1•]**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:**

1. Reaction of acute onset with skin-mucosal involvement and at least one of the following:
 - (A) Upper or lower airways involvement
 - (B) Reduced blood pressure, syncope, or collapse
2. Reaction with two or more of the following that occur rapidly after exposure to a likely allergen for that patient
 - (A) Mucocutaneous compromise
 - (B) Upper or lower airways involvement
 - (C) Reduced blood pressure, syncope, or collapse
 - (D) Gastrointestinal symptoms
3. Reaction with reduced blood pressure after exposure to a known allergen for that patient

Underdiagnosis of anaphylaxis is common, and misdiagnosis has been reported in hospitalized children [34•]. On the other hand, overdiagnosis of anaphylaxis can also occur, particularly in patients with acute multi-system symptoms after ingestion of caustic substances, with foreign body inhalation, and those with acute angioedema or urticaria [35•].

There is not a standard clinical presentation pattern, since it differs from one patient to another. Even when the same patient presents two anaphylactic reactions, they are frequently different in terms of clinical symptoms and signs. In a Spanish study, a basic educational intervention for triage nurses from a pediatric emergency unit led to an increase in the number of patients correctly diagnosed as having anaphylaxis and to a decrease in the waiting time until physician evaluation [36].

Serum tryptase levels in blood samples taken 15–180 min after symptom onset can support the clinical diagnosis of anaphylaxis. Even when tryptase levels are within the normal reference range, other mediators of inflammation such as histamine, PAF, PGD₂, and LTE₄ can be elevated in anaphylaxis [1•, 30, 37].

Diagnosis of eliciting drug

Beyond the clinical history, etiologic diagnosis may include skin testing, drug provocation tests, the measurement of serum-specific IgE (sIgE), and/or basophil activation test (BAT). Regarding the two most important drug groups, BL antibiotics and NSAIDs, all tools have already been evaluated [32•].

Although BL-induced anaphylaxis involves IgE, sIgE has a low sensitivity and BAT is not available in many countries for routine clinical practice. Skin testing is the most important tool and, when negative, challenge tests with the drug implicated or an alternative BL can be indicated [33]. It is crucial to point out that skin testing with commercial benzylpenicilloyl polylysine (PrePen) has now also been validated in children [38].

For NSAID-induced anaphylaxis, it is very important to define, primarily through the clinical history, if the patient is cross-intolerant (non-immunologic anaphylaxis) or a selective-reactor (IgE-mediated anaphylaxis). For selective reactors, most of them allergic to pyrazolones (e.g.,

metamizol/dipyrone), both skin testing and BAT are accurate. Moreover, challenge with another NSAIDs not chemically related to the eliciting NSAID (acetylsalicylic acid, for example) can help to define the phenotype of that patient. If a patient is cross-intolerant to NSAIDs, paracetamol rarely triggers symptoms and a challenge with a cyclooxygenase-2 inhibitor (etoricoxib or celecoxib) can be performed to provide a safe alternative [26, 29, 32•]. Ninety-five percent of these patients are tolerant to paracetamol and cyclooxygenase-2 inhibitors.

In cases of anaphylaxis induced by other drugs, specialists can investigate the possibility to perform skin testing with the drug and, in selected cases, to perform a challenge under deep medical supervision [19•].

Treatment

Anaphylaxis is an acute systemic hypersensitivity reaction and epinephrine is the drug of choice for treatment [39]. Epinephrine has to be used as soon as anaphylaxis diagnosis is made. Correct dose in children is 0.01 mg/kg (until 0.3 mg), intramuscularly (IM) in the thigh. It has been shown that early injection of epinephrine in food-induced anaphylaxis, defined as initial injection before emergency department arrival, significantly reduces the likelihood of hospitalization, compared with initial epinephrine injection after emergency department arrival [40].

In a recent review, authors found that prescription of IM epinephrine for anaphylaxis varied from 23.8 to 93.8% in different countries [31]. In a large case series including 573 patients, 301 received at least one dose of epinephrine. There were four overdose events, all in adults when epinephrine was administered as an intravenous (IV) bolus. Thus, cardiovascular adverse events were more frequent after IV injections. They occurred in 10% of IV epinephrine administrations, whereas only in 1.3% of IM injections and none of these were severe [41].

Despite the mechanisms involved in anaphylaxis fatalities make adrenaline the most important drug to be administered promptly after the syndrome is recognized, it continues to be neglected, even when anaphylaxis is recognized [19•]. Reasons for underutilization of epinephrine mostly include less severe anaphylactic reactions, misperception of some contraindications to use it, or patient's refusal to receive it [42]. It is crucial to remark that there is no absolute contraindication to epinephrine use in anaphylaxis [30]. Some international guidelines concur that H1-antihistamines, H2-antihistamines, and glucocorticoids are second-line or even third-line medications in anaphylaxis [30]. These medications are not life-saving and should not be used as exclusive treatment, despite the fact that they should be used after epinephrine injection.

Anaphylaxis management in the pediatric population has some particularities. Children are usually cared by a layperson, so they should be dismissed with a clear and individual action plan, so that caregivers would be able to recognize severe reactions and treat them rapidly. This action plan should include all relevant information about symptoms and their medication management, that is, when and how to use antihistamines, corticosteroids, bronchodilators, and adrenaline. The recommendations for treatment are based on

increasingly high-quality evidence [3••, 43].

Recurrence of drug-induced anaphylaxis is usually higher in adults (up to 20%) than in children [43]. Nevertheless, children with a history of hospitalization due to anaphylaxis are at higher risk of recurrence. They require a medical follow-up by an allergist [3••].

Conclusions

Drug-induced anaphylaxis seems to be increasing in the pediatric population, and it is associated with a higher severity compared with other agents. Anaphylaxis is still underdiagnosed and undertreated. Pediatricians should be aware of this life-threatening clinical syndrome to promptly recognize it, adequately manage it, and refer patients for allergologic evaluation.

Compliance with Ethical Standards

Conflict of Interest

Ana Carolina D'Onofrio-Silva declares that she has no conflict of interest. Pedro Giavina-Bianchi declares that he has no conflict of interest. Jorge Kalil declares that he has no conflict of interest. Marcelo Vivolo Aun declares that he has no conflict of interest.

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.

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