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Diagnosis and management of drug-induced anaphylaxis in children: an EAACI position paper.

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Introduction

Anaphylaxis is a sudden onset life-threatening systemic hypersensitivity reaction, which is considered to be the most severe manifestation of allergy (1, 2). Anaphylaxis has rightfully received a lot of attention in the recent years and an international consensus has been recently published (3). The most recognized cause of anaphylaxis includes food allergy, drug allergy and hymenoptera venom allergy (3). Differences have been reported concerning triggers and frequency of the clinical manifestations between adults and children. In children, food allergy ranks as the most common allergenic trigger, as confirmed by a recent study reporting on 1970 pediatric anaphylaxis cases. In this study, drugs were reported to be involved in only 5% of the collected cases of anaphylaxis (4). Whilst drug-induced anaphylaxis is commonly reported in adulthood, less is known about the role of drugs in pediatric anaphylaxis. This manuscript aims to review published data on drug-induced anaphylaxis in children focusing on epidemiological aspects, incriminated drugs, clinical manifestations and management.

Epidemiology

The major issue regarding data on prevalence and incidence of drug-induced anaphylaxis is the use of different definitions which make comparisons between studies difficult. There is also great variability in the outcomes used to describe anaphylaxis, these including Emergency Department visits, hospital admissions, specific databases and adrenaline prescriptions (5-7).

In addition, an accurate diagnosis of anaphylaxis in children can prove challenging. This is partially due to the inability of children to accurately describe their symptoms, the lack of cutaneous symptoms in up to 40 % of drug-induced cases, the lack of tryptase measurement in most cases and difficulties in accurately evaluating blood pressure, especially in infants (8-12). A recent work on paediatric anaphylaxis presenting at an ED showed that almost 50% of the diagnosis are actually missed (13). Thus, reports on general anaphylaxis incidence in paediatric ages have a wide variation in number from 10.5 to 70 episodes per 100,000 person-years (14, 15). The majority of studies report that the rate of anaphylaxis has increased over the last decades in all age groups, with increased risk of worse outcome in teenagers/young adults, in those with co-morbidities such as asthma and more severe reactions in the case of drug-induced episodes (5, 16-19). A recent US retrospective study on ED visits for anaphylaxis (2005-2014) reports increasing rates in all age groups with the greatest increase observed in children aged 5-17 years (196% increase). The rate of food-related anaphylaxis increased by 124% and the rate of medication-related anaphylaxis increased by 212% (18).

Biphasic allergic reactions, occurring after initial recovery, were reported in up to 15% of children presenting with anaphylaxis (4, 20-22) and the rate maybe higher for drug-induced reactions (23).

Data on fatal anaphylaxis are generally scarce. In an Australian study reporting both on children and adult patients, the causes of anaphylaxis fatalities were drugs, or “probably” drugs, in 58 % of the cases (24). Besides, in the US, a significant increase in fatal drug-induced anaphylaxis over 12 years: from 0.27 per million in 1999-2001 to 0.51 per million in 2008-2010 was noticed and medications were found to be the most common cause of anaphylaxis-related deaths both in adults and children (25).

A retrospective study on anaphylaxis reporting on 108 pediatric cases admitted in a children’s hospital revealed a 2% fatality rate. In this study 25% of the anaphylactic episodes were drug related, but none of the fatal cases were caused by drugs (21). Cardiovascular symptoms and shock are more frequent among adult patients compared with children and/or adolescents (26). Nevertheless, some data also indicate that cardiovascular compromise may occur more frequently in children with drug-induced anaphylaxis, as compared to food- or insect sting-induced anaphylaxis (11, 23, 27).

Data released from the European Anaphylaxis Registry in 2016 on 1970 children with anaphylaxis reports that only 101 cases (5%) were drug-induced (4). However other reports give a different perspective of the importance of drug-induced anaphylaxis in pediatric populations showing an increasing importance of drugs according to age.

In a multicentre Turkish study reporting on 224 cases (137 children) of pediatric anaphylaxis, drugs were involved in 47 episodes (21.0%). Comparing results according to age groups and etiology, the rate of food-induced anaphylaxis was significantly higher in the 0–2 years and 3–6 years age groups (OR: 25.6, and OR: 5.7, respectively),

while hymenoptera venom anaphylaxis was higher in the 7–11 years age group (OR: 3.6), and drug-induced anaphylaxis was higher in the 7–11 years and >12 years age groups (OR: 2.6 and OR: 2.9, respectively) (28).

A Brazilian study reporting on 191 pediatric patients with previous anaphylaxis also showed the increasing importance of drug-induced cases in parallel to age and revealed that drugs are the major causative agents after the age of 12 years being responsible for 44% of the anaphylaxis cases (29).

In another Turkish study on pediatric anaphylaxis in children, which included 96 patients seen at a pediatric allergy clinic in a tertiary care centre, 27% of the cases were attributed to drugs (30) and, in another report on 34 cases of severe anaphylaxis in children seen in a pediatric allergy department, 61.8% of the cases analysed were caused by drugs (19).

A Thai study on anaphylaxis in children reporting on 172 episodes found drugs as being implicated in 33% of the cases (23) and the same percentage was found in a case series from Singapore (27).

Two Portuguese studies on pediatric anaphylaxis reported drugs as causative agents in 8% (31) and 11% (32) of the cases.

A 2017 systematic review on the prevalence of self-reported drug allergy (pooled sample of 126,306 participants) showed that anaphylactic and systemic reactions were reported by 10.8% of participants reporting a drug allergy. In studies specifically assessing anaphylaxis, the frequency was 7.6% among children and 9.3% in adult participants (33).

Culprit drugs

Most data on anaphylaxis epidemiology in children concern anaphylaxis in general and does not focus on drug-induced cases in particular, making difficult to evaluate the real importance of drugs as causative agents.

Administration of any drug at any dose can potentially cause anaphylaxis. But in children, NSAIDs and antibiotics are the most frequently incriminated drugs (26). This higher prevalence of allergic reactions to these drug classes as compared with others is probably related to the high and global prescription rates of these drugs in children.

Antibiotics, and particularly beta-lactams, have been identified as the main causes of drug-induced anaphylaxis in children in several studies (11, 34). Regarding non-betalactam antibiotics, few cases of anaphylaxis to macrolides have been reported in children to date. Thus, azythromycin-induced anaphylaxis has been confirmed by skin testing in three children (35). NSAIDs anaphylaxis is at the second rank as triggers of pediatric drug-induced anaphylaxis. Of note, NSAID hypersensitivity ranks at the first place in few epidemiologic studies (26, 29, 31, 36).

Ensina et al. reported dipyrone as the main cause of NSAIDs-induced anaphylaxis, followed by ibuprofen (75%) and acetaminophen (50%)(37). Faria et al reported ibuprofen as the main cause of anaphylaxis followed by ASA and paracetamol (38).

In Singapore records of 485 pediatric cases presenting with anaphylaxis to the pediatric emergency department (2007-2014) were analyzed and ibuprofen-induced anaphylaxis was the most common cause among drug-related cases (39 patients, 47.6%). (39)

In general, preferential Cox-1 inhibitors seem to play a major role in NSAIDs-induced anaphylaxis.

As shown in a recent study from Portugal on drug-induced anaphylaxis based on 87 reported cases, suspicion of hypersensitivity to vaccines is also found in children (40). However, real immediate hypersensitivity reactions to vaccines remain rare, ranging from 1 in 50,000 to 1 in 1,000,000 doses (41, 42).

Concerning anaphylaxis occurring in special settings, such as anaesthesia, the importance of drug predominates. In this particular scenario, a French pediatric study, referring to a 12-year period, estimated the frequency for IgE-mediated anaphylaxis as one in 2100 anaesthetic procedures; neuromuscular blocking agents (NMBA) and latex being responsible for most of the reactions followed by antibiotics and NSAIDs. This high incidence was partially explained by their biased population that included of a large number of children with congenital malformations requiring repeated interventions (43).

In a more recent study the overall incidence of peri-anaesthetic anaphylactic reactions was estimated at 1:7741 procedures and the incidence to NMBAs reactions was 1:81275 (44). In this study, latex, and not drugs, was the most identified agent confirming results from other reports on perioperative anaphylaxis in children (45).

Risk factors

A previous history of an anaphylactic reaction, co-existent asthma, atopy, and atopic diseases are reported to be major risk factors for anaphylactic reactions in general both among adults and children (22, 46, 47).

However, the role of atopy as a risk factor for pediatric anaphylaxis may differ according to eliciting agents. In a retrospective multicentre study including 224 episodes of anaphylaxis in children, risk factors were analysed according to etiologic agents. The rate of atopic diseases was significantly higher in children with food anaphylaxis (OR: 3.9, 95% CI: 1.6–9.7) and significantly lower in children with hymenoptera venom anaphylaxis (OR: 0.2, 95%CI: 0.09–0.5). In this study asthma, atopy or atopic diseases were not identified as significant risk factors for anaphylaxis due to drugs and medications (28). Also in a study reporting on 485 anaphylactic reactions in paediatric patients no statistically significant association between severe anaphylaxis and the type of trigger or a past history of atopy was found and the only independent predictor for severe anaphylaxis was a previous report of drug allergy (39).

Another report on 264 cases of drug-induced anaphylaxis including 49 children actually found that severe reactions were less frequent if there was an underlying asthma (38.6% vs 61.4%) or atopy (43% vs 59%). (26)

The role of atopy in the case of perioperative anaphylaxis has not been demonstrated neither in adults nor in children (45).

Considering the role of previous events as a risk factor, it is also important to emphasize that up to 65% of children presenting with anaphylaxis do not report a previous reaction (21, 48).

Regarding demographics, anaphylaxis of all causes as well as drug-induced anaphylaxis is more common in boys in the pediatric population, which is different from the adult population (4, 21, 40, 49). Even the usual female predominance seen in perioperative anaphylaxis is not observed among pediatric patients (45).

Mastocytosis is another reported risk factor for anaphylaxis in adults as well as in children. In a study on anaphylaxis in patients with mastocytosis, the cumulative incidence of anaphylaxis in patients with mastocytosis was higher in adults (49%) compared to children (9%). However, in children, study inclusion was limited to those with severe disease, extensive skin involvement and/or high tryptase levels. In this series, one child among 46 mastocytosis pediatric cases had anaphylaxis due to a vaccine administration. It was recommended that children with severe disease and/or previous anaphylaxis should be provided with an emergency medication (50).

A recent Spanish study showed that the frequency of perioperative anaphylaxis appears to be higher in children with mastocytosis compared to the general population (51). Yet a work comparing serum basal tryptase levels in children with different severity of drug hypersensitivity reactions with age-sex-matched controls without history of DHRs found that levels of drug-hypersensitive patients with and without anaphylaxis and the control group were similar (52). As data on the contribution of different risk factors in the case of drug-induced anaphylaxis in children is inconsistent and sometimes contradicting this seems to be a field that needs further exploration in future research.

Diagnosis

i) Differentiating anaphylaxis from other acute drug-induced adverse reactions:

The diagnosis of drug-induced anaphylaxis is based primarily on clinical signs and symptoms; for many scenarios e.g. peri-anaesthetic reactions, the clinical notes and a detailed description of the acute episode are essential. It is important to distinguish anaphylactic reactions from other clinical manifestations that occur coincidental to drug administration such as vasovagal responses or the oculo-respiratory syndrome (ORS),

which has been described after influenza vaccine administration and characterized by bilateral conjunctivitis, facial oedema and upper respiratory symptoms (53).

A diagnosis of anaphylaxis is highly likely when any one of the criteria listed in Table 1 is fulfilled (1, 54-58).

The majority of drug-induced anaphylactic episodes include cutaneous symptoms; however, their absence should not rule out anaphylaxis, as dictated by the criteria system. Laboratory tests are generally not useful for the acute diagnosis of anaphylaxis, although serum histamine and tryptase may be of help. Serum histamine level rises quickly with the onset of symptoms, but does not remain elevated after 30-60 minutes.

It is thought that serum tryptase is more frequently elevated with drug-induced as opposed to food-induced anaphylaxis. Whilst this may be an allergen specific effect it may also relate to dose and route of administration with many drug-induced anaphylactic events occurring after intravenous medication administration. Serum tryptase level peaks 60-90 minutes after the onset of symptoms and remains elevated for up to 5 hours. β -tryptase is released with degranulation of mast cells, whereas α -tryptase is secreted constitutively by the mast cells. The ratio of total tryptase to β -tryptase can help distinguish systemic mastocytosis from anaphylaxis. A ratio ≤ 10 implies anaphylaxis, whereas a ratio ≥ 20 is consistent with systemic mastocytosis (59).

ii) Confirming or identifying a drug-induced trigger

Four to 6 weeks after recovery, according to the ENDA (European Network on Drug Allergy) EAACI guidelines, *in vitro* test (specific IgE or basophil activation test) and/or *in vivo* tests should be undertaken, in order, to identify the eliciting drug (60, 61). However, for children, these diagnostic methodologies are not substantiated with high quality evidence. Current guidelines recommend the use of skin tests, for certain drugs (60, 61). Generally, intradermal tests with drugs are poorly standardized, logistically

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demanding, and relatively painful procedures and are therefore performed less frequently in infants and children compared with older age groups (62). There are guidelines published that detail recommended concentrations for skin tests with various drugs (62). Thus, although validated reagents for skin testing are limited (e.g. penicillins, NMBA's), other medications can be tested by using non-irritating concentrations of the relevant drug. However for most drugs, skin tests lack the predictive power to change clinical decisions at this point. Initial testing with higher dilutions and slow titration to regular test concentration are generally recommended (63). Most of the data in current recommendations arises from adult studies with only few data specific for children are published (64, 65). However, differences between children and adults have been highlighted. For example, the rate of systemic reaction during skin testing with beta-lactams has been found to be lower in children than in adults, and several reference center used directly the full dose for skin testing (66). Further studies are needed to evaluate the real diagnostic value of those tests and the optimal protocol in the pediatric population. This is also scant evidence to validate the use of serum specific IgE to the available drugs (67).

In the vast majority of cases, a drug provocation test should often be discussed to confirm or exclude an immediate-onset drug-induced hypersensitivity. DPTs are primarily indicated in patients in whom the clinical suspicion of drug allergy is low. In a child with a likely diagnosis of drug-induced anaphylaxis, DPTs should not be performed to the culprit drug unless a clinical imperative to do so. If presenting symptoms are highly suggestive or severe in nature, the diagnostic challenges may then aim to identify safe alternative drugs for future use. Various protocols have been proposed but again, no specific protocols for children have been developed (60, 61, 67). It is important to note that skin testing and provocations tests should take place in safe,

well-equipped and trained outpatient settings; in case of high risk (previous anaphylaxis), close supervision in a hospital settings is required(63).

Regarding vaccine hypersensitivity, specific guidelines including testing with the different vaccines components as well as vaccine itself have been recently published (68, 69).

Management

Management of the acute event of drug-induced anaphylaxis in children

Anaphylaxis has been defined as a severe life-threatening allergic reaction. The immediacy of reactions and life threatening nature warrants immediate treatment. The management of drug-induced anaphylaxis is similar to other scenarios, regardless of the inciting mechanism or cause. In a medical setting, it is imperative to have a protocol available including appropriate pediatric dosing and resuscitation equipment, and staff should have undergone training in the identification and management of the pediatric patients presenting with anaphylaxis. EAACI guidelines for the management of anaphylaxis have been published in 2014 providing a protocol for general management during the acute phase of patients developing anaphylaxis (3). Briefly, the protocol should include the following important points (3):

- First line treatment includes intramuscular adrenaline before initiating other interventions. Inject adrenaline (epinephrine) intramuscularly in the mid-outer thigh at a dose of 0.01 mg/kg up to a maximum of 0.5 mg in health care settings, or use a weight-appropriate epinephrine auto injector of 0.15, 0.3 or 0.5 mg in community settings. Dose may be repeated in 5-15 minutes. If cardiorespiratory arrest occurs cardiopulmonary resuscitation should be immediately instituted.

- Second-line intervention include removal of the trigger after having made a clinical diagnosis of drug-induced anaphylaxis and promptly call for a trained pediatric resuscitation team if available. In addition, patients experiencing an anaphylactic reaction should be position properly and high flow oxygen should be administered. For patients with cardiovascular instability, fluid support should be initiated promptly and inhaled short-acting beta-2 agonists can be additionally given to relieve symptoms of bronchoconstriction.

- The third line interventions include mainly administration of H1- and H2-antihistamines, and glucocorticoids that are thought to prevent protracted anaphylaxis symptoms or bi-phasic anaphylaxis. Of note, theoretically at least, glucocorticoids may play a role in the treatment of drug-induced anaphylaxis by NSAID where the putative mechanism may be the release of active eicosanoids (61). However, these medications should not be used as a first step treatment or as mono-therapy because they do not rapidly reverse laryngeal oedema, bronchospasm, or hypotension (70, 71).

The duration of observation can be tailored to the individual clinical scenario and guided by the severity of the reaction, response to treatment, comorbidities (e.g. asthma, cardiovascular compromise), and the relative half-life of the putative eliciting drug. It is recommended to observe the patient for at least 6-8 hours in case of respiratory compromise and at least 12-24h hours for patients who presented with hypotension. This will facilitate the recognition and treatment of bi-phasic reaction which may develop after complete recovery of anaphylaxis with no further exposure to the allergens in 0 to 15 % of the children. Monitoring of blood pressure, heart rate and function, respiratory status and oxygenation at frequent and regular intervals or continuous monitoring where possible is also recommended.

Management of drug-induced anaphylaxis in children, after the resolution of the acute event

When the acute reaction has resolved the health care providers attention must then move to notification of the suspected drug allergen and investigation. (Figure 1). Specific aspects of drug allergy should be taken into account. Children with suspected drug-induced anaphylaxis should be promptly referred to a specialist allergy centre proficient in the diagnosis and management of drug hypersensitivity in this age group. A complete allergic workup as described above will be performed to confirm or exclude the diagnosis, but also to identify safe alternatives if the allergy is confirmed.

Once a diagnosis is established and a specific drug (or drug family) is implicated, complete avoidance of the drug is the safest choice. For most cases, after diagnosis, there is no need for providing injectable epinephrine as part of the emergency plan. For a subgroup of patients with multiple drug allergy phenotype, where the risk of reaction to unrelated drugs is increased, but also for patients in which the diagnosis has not been confirmed by a complete allergic workup, providing injectable epinephrine to parents/patients might be recommended. Clear communication between patient, families and all health care providers is the key to safe management, not only on which drugs to avoid but also on safe alternatives. A medic alert bracelet or other recognizable wearable alert may be recommended for children in educational settings.

If no suitable therapeutic alternative (preferably from a different class) is available, desensitization to the culprit drug conducted by experienced health care professionals maybe attempted.

Desensitization Protocols

Rapid desensitization is used clinically to prevent the occurrence of a severe allergic reaction in sensitized patients, when substitutions with an alternative are not possible.

It enables a temporary induction of tolerance that is maintained for the duration of exposure to the drug. Many protocols for rapid desensitization have been published for different types of drug classes, most following a general theme of doubling doses at short intervals over several hours, although few have been tried or published in the pediatric age group (72, 73).

For children with positive allergic workup after suspicion of anaphylaxis to vaccine, the vaccine can still be administered in graded dose according to the protocol proposed by the American Academy of Pediatrics (68, 69).

Follow-up

The natural history of drug hypersensitivity with most drug classes in children is largely unknown. Some IgE mediated penicillin allergy will resolve with time, however, resensitization upon exposure has been documented (74). Anecdotal information also exists that children with NSAID-exacerbated cutaneous disease (NECD), may resolved their NSAIDs hypersensitivity, when the urticaria abates (75).

Conclusion

Drug-induced anaphylaxis remains rare in children, but associated with a life-threatening risk. In consequence, correct identification of these patients is of major importance, not only to avoid severe reactions, but also to decrease the number of children falsely labelled as allergic. There is a need for large, multicentric studies, to evaluate the real diagnostic value of the currently available skin tests especially

concerning anaphylaxis. Moreover there is also a need to develop new diagnostic tests in the future in order to avoid drug provocations and to improve the management of these children.

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Table 1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled following exposure to an allergen-drug:

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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)
-

2. Two or more of the following that 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 GI symptoms (e.g., painful abdominal cramps, vomiting)
-

3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP*PEF = Peak expiratory flow; BP: blood pressure; GI: gastrointestinal

* Low systolic blood pressure for children is age specific and defined as: < 70 mmHg for age 1 month to 1 year; < 70mmHg + [2 x age] for age 1 to 10 years; < 90mmHg for age 11 to 17 years.

