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Perioperative allergy and anaphylaxis in children : a review

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Abstract. *Objective:* Perioperative allergic reactions in pediatric patients are a known complication in anesthesia. The present review aims to look at the incidence and implication of perioperative allergic reactions in children.

Methods : A review was conducted from electronic databases Pubmed and Cochrane Library. Articles were identified concerning perioperative allergic reactions in children with key words "perioperative allergy children" and "perioperative anaphylaxis children". Elaboration to related articles was based on these documents.

Results : Literature focusing on perioperative allergy in children remains rather limited. Reported incidences are limited and depend on the geographic location, the population's exposure to allergens and the practice of the institution. A protocol for treatment or management in allergic reactions was proposed, based on the available literature.

Conclusions : Allergy in children is less prevalent than in adults. Latex is the number 1 causative in children, especially in the at risk group. Allergy to NMBA (neuromuscular blocking agents), morphine and latex may be overdiagnosed and cross-reactivity of antibiotics is overrated.

Further data, specified to children, should be collected in order to optimize a pediatric allergy protocol.

Key words : anesthesia ; allergy ; anaphylaxis ; pediatrics ; children

During anesthesia, adverse drug reactions may occur. These reactions can be divided in dose-dependent reactions, related to the pharmacological properties of the drug and/or its metabolites, and reactions that are unrelated to the drug's pharmacological properties which are less dose-dependent (1). These reactions include drug intolerance, idiosyncratic reactions and drug-induced, immune-mediated/allergic and non-immune-mediated/pseudo-allergic, reactions. Anaphylactic reactions can be classified into allergic anaphylaxis and non-allergic anaphylaxis, where the allergic reaction can be IgE mediated or non-IgE-mediated (1,13) These reactions are associated with a significant mortality and morbidity, mainly related to an ineffective resuscitation, resulting in cerebral hypoxia (13).

Due to the lack of information about perioperative allergy in children and the differences in practice between institutions and over time, our primary aim was to review the incidence and the implication of perioperative allergic reactions in children.

Epidemiology

The reported incidence of allergic reactions is very variable from country to country, ranging from 1:385 to 1:20,000 depending on the geographic region (2,3,4,5,9,13,15). In children this incidence is 1:2100-1:7700 (6,13). Allergens differ according demographics, genetics, anesthetic practices and difference of drug use in each country (7). In general, 30-60% of the peroperative anaphylactic reactions are IgE-mediated reactions, with a mortality rate of 3-10% in Europe (2,8,9,10,12,13). Where neuromuscular blocking drugs are reported as the most frequent likely causative agents of perioperative immunoglobulin IgE-mediated in some European countries and Asia, a similar pattern can be seen in some regions of the United States, although antibiotics are playing a mayor role as well (2,6,8,11,13,14). The same products are responsible for anaphylactic shock in infants, however, the number one cause of the intraoperative IgE-mediated reactions in children remains latex

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Table 1
Severity of anaphylaxis

	Severity of reaction	**Implication during anesthesia**
Grade I	Cutaneous signs	Difficult to diagnose due to the covering sheets
Grade II	Moderate multi-organ involvement, non-life-threatening	Small hemodynamic or respiratory repercussions cannot be reported by the patient during general anesthesia and may be missed
Grade III	Severe life-threatening multi-organ involvement, requiring treatment	May be difficult to differ allergic symptoms from anesthethic effects, blood loss and sensitive airways
Grade IV	Circulatory or respiratory arrest	May be difficult to differ an allergic cause from other causes (blood loss, vagal stimulation, anesthetic overdose,..)

allergy (up to 76%) (6,9,11,12). In contrast, the 12-year survey of Karila did identify neuromuscular blocking agents as the main cause for IgE-mediated reactions (NMBA in 60.8%, latex in 27%, colloids in 14%, opiates in 9% and hypnotics in 12%) (13).

Definition and pathophysiology

Allergy is defined as the reaction, existing in objectively reproducible symptoms or signs, which are initiated by exposure to a stimulus at a dose tolerated by normal individuals (6). Where anaphylaxis is defined as a clinical syndrome characterised by sudden onset and rapid progression of signs and symptoms, involving multiple organ systems.

Allergic reactions can be divided in IgE mediated and non-IgE-mediated reactions (13). 60-70% of the immediate hypersensitivity reactions that occur during anesthesia are IgE mediated (9). The clinical manifestations in patients with true IgE-mediated anaphylaxis appear more severe and the severity can increase with subsequent administration (2,12,13). Non-IgE-mediated reactions are hard to distinguish from an IgE-mediated reaction in the clinical setting and they do not require previous contact (12). Other mechanisms may be responsible, they include complement activation, direct histamine release or direct activation of mast-cells (8). Regardless of the triggering mechanism (immunologic or non-immunologic), mast cells and basophils play an important role in initiating and amplifying the acute response (14).

In general a history of previous drug allergy in anaphylactic patients is very variable, from 7-29% (15). Additional risk was identified in people who are on beta-adrenergic blockers or known to be atopic, up to 25% of the anaphylactic cases were atopy related, where atopy is defined as the symptom complex of rhino-conjunctivitis, asthma, and/or eczema (1,2,6,15). However, other studies suggest that preoperative allergy did not seem to result in an increased risk of perioperative anaphylaxis, but it may favour non-specific release of histamine (7,13).In children, no significant differences were observed in gender distribution, nor in IgE- nor in non-IgE-mediated reactions. Clinical manifestations were more severe with IgE mediated reactions, similarly as in adults. Observations regarding to atopy, asthma or drug intolerance were similar to adults. However, a larger number of IgE-mediated reaction was seen in atopic children who were sensitized to latex and in relation to a positive history of food allergies (12). Compared to adults, higher titers of IgE are found in children, suggesting that children develop higher levels than adults (21).

Table 2
Level of anaphylaxis

	Signs and symptoms
Level I	≥ 1 major dermatological and ≥ 1 major cardiovascular and/or respiratory
Level II	≥ 1 major cardiovascular and respiratory criteria or ≥ 1 major cardiovascular/respiratory and ≥ 1 minor criteria involving different systems
Level III	≥ 1 minor cardiovascular/respiratory criterion and ≥ 1 minor criterion from each of ≥ 2 different systems

Most of the symptoms develop within 30 minutes after administration of the drug. Allergic reactions most commonly present in cutaneous manifestations (69.6-93%), severe hemodynamic manifestations (20-81.6%) and bronchospasm (11.6-44.2%) (2,15). Absence of dermal symptoms does not exclude an allergic mechanism (2,9,12). On the other hand, a reaction with only one clinical presentation can easily be missed. Clinical manifestations are commonly divided in 4 grades of reactions (Table 1) and 3 levels of severity (Table 2) (2,7,15,16,25). Majority of allergic reactions involved grade II and III reactions, respectively 23% and 60%, where non-allergic reactions were grade I and II, respectively 55% and 30% of the reactions. Grade IV was only seen in true anaphylaxis (6%) (2). Prediction if a reaction was IgE-mediated, based on clinical manifestations, remains difficult (25). Allergic reactions in general are more reported in females than in males (7,15,26). Not all studies could statistically associate gender

difference with the allergic reaction mechanism or the causative agent (2,24). Where reactions to anesthetics (induction agents, NMBAs) and antibiotics occur immediately, within 5-10 min after injection and reactions to dyes or latex tend to have a delayed onset (up to 30 min-1 hour or more) (1,9,12,20). Delayed reactions are not frequently caused by anesthetic agents, most associated to local anesthetics, heparin, antibiotics, antiseptics and contrast media (2,9).

Frequently implicated allergens

Latex

Certain medical products contain latex, which is composed of spherical poly-isoprene droplets coated with a layer of water-soluble proteins. Latex can cause a IgE-mediated sensitivity in sensitized patients, but in addition it also may be responsible for an allergic contact dermatitis (type IV hypersensitivity) (2,19). A clinical non-immune-mediated reaction is also possible, resulting in irritant dermatitis with a mild irritating effect (19). Latex sensitivity in the pediatric population is reported between 0.3-4% (6). The frequency in children undergoing multiple surgery ranges from 16.7 to 76% (1,6,13,17). A Norwegian study published a percentage of only 3.6% of the cases of perioperative anaphylaxis due to latex, probably resulting in the large use of a latex free environment, including un-powdered gloves (1,6). Latex is the most frequent diagnosed cause of IgE-mediated reactions (41,8%) in children. Per anesthetic allergic reactions related to latex were fatal in 5-7% of the cases, of which 4% would have had an earlier undiagnosed preoperative allergic reaction (18). Preoperative screening for latex allergy is recommended in high-risk groups which includes neural tubes defects and urologic, gastrointestinal and tracheoesophageal anomalies, repeated and early exposure, multiple surgeries (>5-8) previous placement of a gastrostomy tube, atopy and female sex (1,6,11,17,18,19,20,21). 28 to 67% of spina bifida patient may have a history of latex allergy and 47% show evidence of sensitization (latex-specific IgE) (6,22). A set of polypeptides of latex allergens have been defined as primary allergens by the International Union of Immunological Societies (6). A subset have been related spina bifida patients and patients with urological congenital anomalies, as well as with health care workers (6,17,19). Investigation of several candidate genes have also been achieved concerning their role in predisposing children with spina bifida to latex hypersensitivity, no associated was withhold in children with spina bifida, suggesting that environmental factors had more influence in this population than genetic predisposition (13,15).

The onset of an anaphylactic reaction on latex in the operation room occurs within 25-290 min after induction, when latex gloves are in direct contact with large surface areas within a body cavity (13,15). Children tend to present with hypotension, tachycardia and bronchospasm, less frequently noticed with cutaneous manifestation and rarely with cardiovascular presentation as bradycardia and cardiac arrest (13). Most perioperative reactions are grade 2 or higher, a grade 4 reaction is rarely observed in children (13). In the anamnesis of latex allergy, cross sensitivity for certain fruits (banana, kiwi, papaya, chestnut, avocado), vegetables (tomato, carrot, bell pepper, raw potato) and Ficus tree should be questioned (13,17). 11% of the people with fruit allergy would have latex allergy, similar the risk of fruit allergy in patients with a known latex allergy is 7% (6,13). It is understood that latex sensitivity precedes latex fruit sensitivity (13). Clinical history of latex history was only present in about 30-50% of the cases before in-hospital presentation of whom experienced grade IV reactions (anaphylaxis) (18,21). In addition, higher risk is found in patients with childhood asthma, repeated allergies or atopy, where 8% of the adult population is latex sensitive (6,9). Children with latex allergy should be scheduled as either the first of the day or after the room has been free from latex exposure for at least 90 minutes, ideally 2.5 h, after 2.5h the concentration would reduce to 4% of the average room concentrations of latex (13,15). One study even reported significant aerolized latex antigen 5h after the last use, a time break incompatible with a normal surgery schedule (15). It may even be more cost effective to avoid latex-containing products than to disburse all the additional costs of treatment, diagnosing and reimbursing the incurred disabilities and fatalities (13,15). The main difficulty here is the presence of hidden latex material, to be traced with the pharmacist to establish a complete checklist (15).

Muscular relaxants

Muscular relaxants can induce 2 types of reactions. One is driven by an immunologic mechanism and is IgE dependent (specific IgE antibodies against NH4+ group), while the second one, in particular with benzylisoquinolinium

neuromuscular blockers, do result from non-specific stimulation of basophils and mast cells (1,26).

In Belgian series, NMBA were the leading cause of perioperative allergy (40-61.9%) (2,25). Similar results were found in France, with NMBAs (50-70%) as first cause, followed by latex (12-16.7%) and antibiotics (8-15%) (12,15). In Spain, antibiotics were the main cause, followed by NMBAs (13). The highest prevalence of IgE-mediated reactions, caused by NMBA is reported in Norway. 93,2% were caused by NMBA (13). NMBAs were the most frequent cause in adolescents as well (31.97%). In general, allergy to muscle relaxants is described to be 10 times more prevalent in adults comparing to children (26). This phenomenon has two possible explanations of which one is that muscle relaxants are more likely to be used in adults. A second explanation is the difference in exposure to the quaternary ammonium epitope, a compound of the non-depolarising muscular blocker, which is also a constituent of many domestic products (cosmetics, detergents), which can also explain the higher prevalence in women (7). Another explanation is the involvement of sex hormones in skewing the immune response towards a Th2 profile (2). A high incidence of allergy to rocuronium has been noted in Belgium and has been declared by an increased rocuronium market share or overestimation due to inappropriate irritating skin test dilutions or false-positive IgE results (2,25). NMBA were also classified depending on their risk of sensitization with suxamethonium and rocuronium as high risk, pancuronium and vecuronium as having medium risk and atracurium and cisatracurium as having low risk (2,8,13). The antigenicity of muscle relaxants is complex, sensitivity to non-depolarising blockers is highly dependent upon presence of the bisquaternary ammonium ions, needed for bridging of adjacent. Other factors, such as, inter-ammonium distance and flexibility of the molecule may be important (26). It appears to be common because of the quaternary ammonium group (1). Cross-reactivity between these products is seen in 60-85% of the patients with 15% reacting to all tested muscle relaxants (1,2,8,26). Certain NMBA's have higher risk than others, where vecuronium would have the highest risk of cross-reaction (87.5%), followed by rocurionium (80.6%), atracurium (76.8%) and suxamethonium (54.3%) according to Mertes et al. (2). Other studies described rocuronium, and cisatracurium as having the lowest cross-reactivity risk (22.3-33% and 13.9%) (2). Cross-reactivity exists not only between NMBAs, but also between NMBAs and narcotics including morphine, codeine and pholcodine which all have a single tertiary ammonium ion (14). Exposure to other products containing a tertiary or quaternary ammonium (drugs, disinfectants, food and industrial materials) can also cause cross-reactivity with morphine or NMBA (14). Use of suxamethonium still poses the greatest risk, this, despite its structural homology to acetylcholine (9,12,26). Nevertheless, it is now a rare cause of allergy as it is not frequently used (2). Skin prick test would be more useful to identify the responsible NMBA, where intradermal test would be more indicated to investigate cross-reactivity (12).

Antibiotics

Allergic reactions to antibiotics are most seen to cephalosporins due to the higher impact in clinical use, but the most common antibiotic allergen remains penicillin (1-3%). Penicillins and cephalosporins account for approximately 70% of perioperative anaphylactic reactions caused by antibiotics (1,12). Cephalosporins would be responsible for about 38% of antibiotic-related anaphylaxis and 27% of the sever β-lactam allergies (23). Reactions to cefazolin were mainly immediate and severe (23). Results in cross-reactivity between penicillin and cephalosporins vary within a wide range (1-25%) (15,23). Cross-reactivity with other β-lactams suggests the implication of the R1 side-chain as an essential role in IgE-mediated reactions to cefazolin. More research on this subject is needed in order to define some clear rules to predict cross-reactivity with other β-lactams (23).

Different algorithms that combine skin tests, IgE and in selected cases provocation tests, are described. Starting with skin prick testing which can be followed by intradermal testing in case of negative results. These test should include amoxicillin, ampicillin, as well as the culprit compounds (1).

Opioids

Allergic reactions to opioids such as morphine, codeine and synthetic opioids (pethidine, fentanyl) are mostly mild IgE-mediated (1.6% in France), but an augmented histamine release can be detected in case of non-immunological histamine release to another product (8,15). Human skin mast cells tend to degranulate in vitro in the presence of morphine, in contrast to human lung and heart mast cells, who do not (1,26). Therefore, opiate mediated systemic

reactions are assumed to occur by an IgE-mediated mechanism or massive mediator release from skin mast cells, or by an altered mast cell phenotype allowing activation of mast cells outside the skin (1,26).

IgE-mediated reactions from opioids are published as case reports with anaphylaxis from fentanyl, meperidine, papaveretum, codeine, morphine and pholcodine. In case of a reaction to morphine or codeine, neither morphine or codeine should be administrated, but all other opioids are permitted (9). Hypersensitivity to these agents are most frequently nonallergic reactions (9). It has been recommended to switch to a different subclass in case of allergy. In none of the anaphylaxis cases is a potential cross-reactivity between different opioid subclasses reported. The subclasses consist in phenanthrenes (morphine, codeine), phenylpiperedines (alfentanil, fentanyl, sufentanil and meperidine) and diphenylheptanes (methadone and propyxhene). Fentanyl appears not to induce nonspecific mediator release from mast cells. Recently, reactions with morphine antibodies of codeine, meperidine and methadone was observed, what doesn't support the practice of switching to another subclass (1).

Diagnose of opiate allergy still remains difficult because skin tests are not useful and morphine IgE does not per se indicate sensitization but may mirror sensitization from NMBA. With basophil activation was observed that morphine and codeine do not trigger basophil degranulation in opiate-tolerant individuals, who tested positive in a solid-phase morphine IgE antibody assay and could erroneously have been diagnosed as opiate-allergic (27). Challenges may also be required to diagnose opioid allergy (1).

Colloids

Today 0.033%-4% of all perioperative reactions are attributed to colloids, which were severe in 20% of the cases (1,8). Due to the difficulty to distinguish hypotension as an allergic reaction or the result of blood loss, this group may be underreported (15). A considerable part of these allergic reactions is attributed to gelatine, which are responsible for 95% of colloid reactions (12,15). Gelatine bound to urea (0.85%) results in more adverse reaction than those with modified fluid gelatine (succinate-linked) (0.33%) (12). We find gelatine in plasma expanders, bound to urea (Haemacel) and as succinylated gelatine (Gelofusine). Diagnosis regarding IgE mediated gelatine allergy can be accomplished with skin tests, IgE quantification or basophil activation test (1).

Dextrans can also induce allergic reactions, called DIAR, dextran-induced allergic reactions. These reactions are mediated by IgG antibodies. Severe DIAR can include bronchospasm, hypotension and cardiac arrest. Hapten dextran is infused before the administration of dextrans in order to avoid this complication, however, reactions still have been reported with the use of hapten dextran (1). Skin prick testing cannot be achieved in case of a suspected allergy, but intradermal testing is described to give positive results (12). Antibodies can be quantified, but these are not readily available (1).

Reactions to hydroxyethyl starches and albumin are more rarely reported.

In general, anaphylaxis from colloids can arise immediately or with a more delayed onset, they generally occur 20 min after start of the infusion (1).

Local anesthetics

Loco-regional anesthesia, considered to be safer than general anesthesia, can evoke a variety of adverse reactions, however reactions are rare and less than 1% have an allergic mechanism (1). We distinguish two groups of local anesthetics: the ester-containing group (bezocaine, chlorprocaine), who can elicit hypersensitivity with important cross-reactivity, and the amides (bupivacain, licocaine), who show little sensitisation and cross-reactivity with each other. Hypersensitivity to local anesthetics is explained in 4 different mechanism: IgE mediated anaphylaxis, complement activation, direct activation of basophils and mast cells and delayed t-mediated urticaria and angioedema (26). The presence of anti-oxidants and presevatives (bisulphites, parabens, carboxymethylcellulose, para-aminobenzoic acid) can also elicit allergic reactions. Challenge tests remain the gold standard for local anesthetics (1).

Hypnotics

Involvement of hypnotics in perioperative anaphylactic reactions is approximately 2% (12). Propofol, is an alkyl phenol, where the two isopropyl groups can act as antigenic epitopes. Testing can be performed by skin tests, IgE and histamine-release tests. In higher doses, a concentration-dependent histamine release from human lung mast cells was described and related to bronchopspam (1).

In case of allergy to egg or soy, propofol can be administrated. The presence of purified soybeen oil in propofol does not contraindicate its use in these patients (9).

Anaphylaxis to thiopental, etomidate (imidazole derviate) and ketamine (phenylcyclidine derivate) is extremily rare (1,8).

Also, midazolam hydrochloride (short-acting imidazobenzodiazepine) is rarely responsible for anaphylactic reactions (8). Testing can be performed by skin and intradermal tests (1).

NSAID

Immediate hypersensitivity reactions from NSAIDS are very common from which a large majority are independent from IgE/FcεRI cross-linking, but corresponding to a pharmacological mechanism (27). Bronchospams and urticaria/angioedema from NSAIDs and aspirin has been explained as a result from the inhibition of cyclo-oxygenase (COX)-1 iso-enzyme with subsequent depletion of prostaglandin E2, unrestrained synthesis of cys-leukotrienes and release of mediators from mast cells and eosinophils (1,8).

Diagnosis of NSAID-related allergy can only be established with provocation tests, more research is necessary regarding diagnostic assays like histamine, cys-leukotrienes release and flow-cytometric testing. In an emergency setting, anti-COX-1 NSAIDS should not be administrated. At the contrary, these patients usually tolerate COX-2 inhibitors.

Antiseptics and contrast media

Chlorhexidine, a frequently used antiseptic and disinfectant, can be involved in IgE mediated hypersensitivity reactions. The presence is hidden in various products, sensitization can occur from home products such as mouthwash or toothpaste (8). Reactions to chlorhexidine can be delayed by 10min (12). Cutaneous application does rarely induce life threatening events. The prevalence of chlorhexidine anaphylaxis would account for 27% of the overlooked perioperative hypersensitivity reactions, depending of the geographic region which can be explained with the different concentration in different countries. In addition, chlorhexidine salts can cause dermatitis and urticaria. Skin testing, intradermal testing, quantification of chlorhexidine-specific IgE and flow cytometric assisted quantification of in vitro activated basophils can be established in the diagnosis of IgE mediated reactions (1,12).

Another frequently used antiseptic, povidone-iodine (betadine), is rarely causing anaphylactic reactions. In case of clinical suspicion, skin test and basophil activation testing can be performed (1). Adding that severe immediate hypersensitivity reactions to radio contrast media (RCM) are estimated at 0.02%-0.04% for non-ionic and 0.1%-0.4% for ionic media, where mild immediate reactions were reported in 3.8%-12.7% for high-osmolar ionic RCM and in 0.7%-3.1% in case of low-osmolar ionic RCM (13,27). Genuine IgE-mediated reactions would account for approximately 4% of the immediate hypersensitivity reactions, which might be overlooked with skin testing. The main pathways of direct histamine release is resulting from non-specific binding of radio contrast media to surface receptor on mast cells or basophils and indirect cell activation resulting from the complement or kinin cascade. The results of skin test and basophil activation testing, with a sensitivity of 46-63% and a specificity of 89-100%, can be complimentary (27).

Preservatives and others

Drug additives such as antioxidants (bisulphites, parabens), emulsifiers (cremophor) and protamine can also produce allergic reactions (26). Additional testing regarding these allergens can be advised.

Diagnosis

The diagnose of an allergic reaction has to be made clinically, after which it can be supported with laboratory findings such as elevated histamine and/or mast cell tryptase (MCT) levels and IgE testing, performance of skin tests and challenge tests if possible (Fig. 1). Simulation has shown that it may take 10 min to make to correct diagnose of an anaphylactic reaction (2). Diagnostic tests are not always readily available, are sometimes poorly validated and do not always demonstrate absolute reliability (25). In addition, multiple sensitization is possible, a Belgian study revealed multiple sensitivity in 7% of the patients (25).

Activated mast cells during an IgE or non-IgE-mediated reactions release tryptase. Human basophils also contain tryptase, but in a 300-700-fold lower level than the mast cells in lung or skin (1,26). Peak serum β-tryptase levels occur approximately 30-60 minutes after the start of the

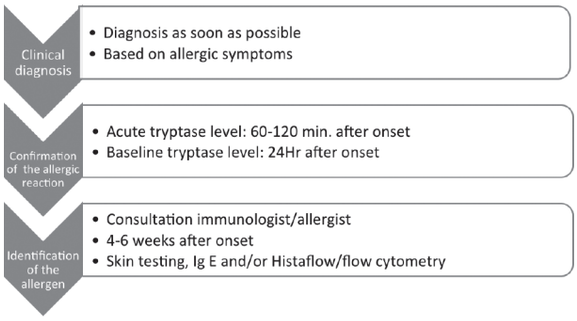

Figure 1:
Diagnosis of an allergic reaction

IgE mediated or non-IgE-mediated reaction, with recommended sampling 60-120 min after onset of the symptoms (1). Different sampling methods are described, where the main goal is to compare the baseline with the highest concentration after an allergic reaction, where tryptase has a half-time around 120 min. A cut-off value of 25μg would be highly suggestive of an IgE-mediated reaction (2,9). Sampling of MCT would have a sensitivity of 64% and a specificity of 89% (12). Concentrations can remain elevated in patients with systemic mastocytosis, mast cell activation syndrome, late-onset reactions, biphasic or protracted cell activation or hematological diseases (1,9). Negative serum testing does not exclude anaphylaxis, false negative results have been distributed to a mechanism where the reaction involves basophils rather than mast cells (1,7,25). False positive results can be seen in extreme stress, like hypoxemia and major trauma (1). Histamine or MCT have a minimal role in pediatric population because of the special handling of the blood sampling of histamine and the rarely elevated titers of MCT in anaphylaxis with predominantly respiratory symptoms, typical for anaphylaxis in the pediatric subpopulation (14).

Allergic testing should be done afterwards to define the allergen, which traditionally consists in using skin tests like prick tests, intradermal allergy test or both, what can be completed with specific IgE testing (14). Allergy tests are feasible and safe in children and have an import value in subsequent anesthetic procedures (24). Skin prick testing is less painful and thus more suitable for children (1). They remain the gold standard in detecting type I reactions (2). The accuracy of these tests is depending of the allergen and the dose that is used (2). Diagnostic work-up of muscular relaxants start with skin prick tests. It is advised to perform skin tests not earlier than 4 to 6 weeks after the acute event because of refractoriness of effector cells and temporarily depletion of specific IgE antibodies (1,9,13).If necessary, the tests can be performed earlier, but this can lead to more false negative results, where on the other hand the sensitivity of skin test might decrease over time, in particular for antibiotics (1,9). When the tests are conducted 6 months or later after the reaction, there is a risk of false negative results, skin test for neuromuscular blockers usually remain positive for a long period of time (1,9) In general skin tests are performed on the anterior part of the forearm with the undiluted drug. When after 15-20 min, a wheal and flare equal or exceeding the 3 mm appears, or an increase in the initial papule of twice or more the size of the initial papule, or at least half the diameter of the positive control wheal, the test is considered to be positive (9,12,26). Sensitivity is described to be good for NMBAs, latex, antibiotics, chlorhexidine gelatine and povidone (12). Skin testing for muscle relaxants is described to between 94 and 97% where intradermal tests for NMBAs are known to produce false positive results because of the ability of NMBAs to induce non-IgE-mediated histamine release (14,26). Some authors doubted whether NMBA are the principal cause of anaphylaxis and whether skin tests can be applied to diagnose allergy from NMBA because of their observations of positive skin prick tests with undiluted rocuronium and vecuronium in healthy volunteers (1). However, this is not confirmed by all authors, where this false positive tests were not whithold (1). Before performing the skin tests, drugs known to inhibit skin reactivity should be stopped some days before testing (antihistamines, psychotropics). Mertes et al described young age, use of β-blockers (except for β-lactams), medium to high dose maintenance or short-term high-dose oral corticosteroids and angiotensin-converting enzyme inhibitors no contra-indication for skin testing (9). This is not supported by all authors (25).

Intradermal testing (IDT) uses injection of 0.03-0.05 ml of commercially available drugs diluted in 0.4% phenol physiological solution with an hypodermic needle, after which we can evaluate after 15-30 minutes (26). A serial dilution is advised starting with a 10^{-4} dilution. Dilutions are progressively increased depending of the drug and only when the results remain negative (1,26). The test is considered to be positive when the size of the wheal exceeds 8 mm (1). Majority of studies describe an optimal timing to perform this testing of at least four to six weeks after the episode, repeated afterwards (14). Intradermal tests with rocuronium should be performed with much lower concentrations to avoid these false-positive

results and interpretation should be done regarding the concentrations used (24,26). Rocuronium and cisatracurium can evoke non-specific positive IDT in nonallergic individuals at concentrations below those currently applied to diagnose anaphylaxis (1).

Specific IgE detecting is possible for a limited amount of drugs and latex (e.g. muscle relaxants, some β-lactam antibiotics, thiopental, propofol, gelatine, chlorhexidine, aprotinin and morphine) (2). It can be executed as the immediate hypersensitivity reaction fades, immediately at the onset of shock, or immediately after induction or during assessment off site (9). The sensitivity of IgE assays in generals is described to be less than these of skin tests, and no substitute of skin testing (2,9). IgE to quaternary ammonium ions has been detected in 3-10% of tolerating patients with no previous reaction and 65-88% of patients with hypersensitivity reactions, reflecting a limited specificity (9). Use of a morphine-based assay has put into question because of the presence of morphine IgE in healthy Norwegian blood donors, a general allergic population (1). For cross-reactivity and identification skin tests remain the standard, functional assays such as histamine release tests or flowcytometric assays can be used as a valuable adjunct (1).

In addition, newer techniques such as analysis of activated basophils can be helpful, especially when skin tests are difficult to interpret. This technique is based on the fact that when basophils are activated by surface receptor FcεRI-bound IgE. They secrete and generate quantifiable bioactive mediators and up-regulate the expression of certain markers which can be detected by multi-color flow cytometry (26). Activated basophils express CD63 in high density, similar to the release of histamine (26). Analysis of CD63 up-regulation on passively sensitized basophils (donor basophils, incubated in patient serum), can suggest the presence of drug-specific IgE antibodies (26). Basophil activation testing is useful in immediate hypersensitivity reactions to diagnose allergy to NMBA, antibiotics, NSAIDs and iodinated radiocontrast media, with a sensitivity that varies between 50 and 60%, and a specificity that attains 80% (except for quinolones and NSAIDS) (27). For latex, this technique showed a sensitivity of 93.1% and a specificity of 91.7% (26). Overall results of the basophil activation test for NMBA have a sensitivity and specificity around 60 and 90% respectively (1).

Basophil activation test for β-lactam allergy was described to have a sensitivity and specificity of respectively, 50% and 94%, higher than these of quantification of IgE antibodies. Use of basophil activation testing should therefore be considered in case of negative or equivocal results of skin test and IgE serology regarding β-lactam antibiotics (27).

Activation of basophils generally is IgE-dependent, but can also be the result from the coupling of receptors with endogenous or exogenous substances and even as result from other, largely unknown mechanisms (27). Therefore, basophil activation testing can be very valuable in case of mediator release resulting from alternative degranulation pathways, for example in case of allergy to quinolones. Especially because of the uncertainty of skin and intradermal testing and the unavailability of well-validated drug-IgE antibody assays (27).

Also histamine release can be quantified with flow cytometry, larger studies are necessary to confirm its potential as research asset (27). Histamine or MCT have a minimal role in pediatric population because of the special handling of the blood sampling of histamine and the rarely elevated titers of MCT in anaphylaxis with predominantly respiratory symptoms, typical for anaphylaxis in the pediatric subpopulation (14).

Another alternative that has been discussed is challenge testing. This risks of life-threatening hypersensitivity reactions are not recommended in routine practice, except for local anesthetics (26). Restricted use has been described for β-lactams, NSAIDS and latex, after a negative skin test (12). For latex, a test with fingertips (15 min) may be performed, which can be followed with an entire glove if the first test is negative (19). In clinical practice, it might be indicated to perform challenge testing with appropriate unrelated compounds in order to find a safe alternative (26). Provocation test may be performed if a negative skin test has not been confirmed and if the clinical history is not suggestive for a severe reaction. Skin testing remains the standard (9).

Treatment

Treatment consists in prevention, treatment and sensibilisation. Where primary prevention is defined as avoidance of an exposure to the drug and secondary is the prevention of the exposure of sensitized patients to their drug or material.

The first step in treatment is withdrawal of the suspected drug or material and to inform the surgical team, followed by administration of 100% oxygen. A patent airway should be maintained, with tracheal intubation where needed (2). Discontinuation of

Table 3
Primary treatment of an anaphylactic reaction in children

Inform the team, request help, stop suspected agents and discontinue anesthesia, Trendelenburg
Maintain the airway with 100% oxygen
For grade II and III
– Volume resuscitation
  - crystalloid at 20 ml/kg
  - colloids at 10 ml/kg, a cumulative dose of 60 ml/kg can be necessary.
– Epinephrine titrated against the hemodynamic response.
  - ≥ 70 mmHg in children up to 12 months,
  - ≥70 mmHg + 2 times the age in children aged between 1 and 10 years
  - ≥ 90 mmHg in children over 10 years old.
    - 1-10 µg/kg
    - bolus 10µg/kg IV in case of collapse
    - continuous infusion starting at 0.1 µg/kg/min up to 1 mcg/kg/min (maximum up to 2-5 mcg)
    - IM: 0.01 mg/kg/dose:

>12 years: up to 0.5 ml (500 mcg) (at 1/1000);
6-12 years (up to 0.3 ml)
< 6 years: 150 µg 1M (0. I5 ml of a I: 1000 solution
– corticosteroids can be used, in asthmatic children early administration is beneficial.
  - 1 to 2 mg/kg of methylprednisolone
  - or hydrocortisone:
    - 200 mg in children aged > 12 years,
    - 100 mg in children between 6 and 12 years old,
    - 50 mg in children between 6 months and 6 years old and
    - 25 mg in children < 6 months old.

– Anaphylaxis with predominance of respiratory symptoms
  - Salbutamol: 50 µg/kg, to a maximum of 1000-1500µg (4-15 puffs), repeated every 10-15 minutes.
  - Intravenous administration as alternative in severe acute asthma
    - 5 µg/kg,
    - followed continuously at 0.1-0.3 µg/kg/min.
    - In practice doses of 0.5 till 5 µg/kg/min,

– For children on B-blockers, with epinephrine refractory shock: glucagon
  - started at 20-30 µg/kg, up to 1 mg
  - infusion rate of 5-15 µg/min

Atropine
- 0.02 mg/kg

Norepinephrine
- 1 mg + 100 ml of glucose serum: 0.01 mg/ml. Start: 0.05 at 1 mcg/kg/min

Dopamine
- 3 mg × weight in kg: mg of dopamine to be diluted in 50 ml of serum
- Dose: 5-20 mcg/kg/min 1 ml/h: 1 mcg/kg/min

Vasopressin
- 0.3-3 mU/kg/min

anesthesia is advised, although volatile anesthetics can be beneficial in solitary bronchospam (2).

It is advised to inject epinephrine intramuscular as soon as possible, with a first dose of 0.3 mg of a 1:1000 solution and to be repeated every 5 to 15 minutes when necessary (28). Epinephrine decreases mediator release from mast cells (28). Further supportive treatment can consist in volume administration and vasporessors (6). The most frequent administrated drugs are depending on the institution: epinephrine (62.5%), antihistaminics (25-48.8%), corticocosteroids (25.6-81.3%), phenylephrine (37.5%), ephedrine (12.5%) and atropine (12.5%) also no treatment was given (up to 34.9% in some institutions) (15).

In emergency situations, regional anesthesia is preferred over general anesthesia and if general anesthesia is chosen, muscle relaxants and histamine-release drugs are advised to be avoided (9). Also latex should be excluded from the environment.

Principles of treating anaphylactic reactions in children are similar to those described in adults (Tables 3 and 4). For grade II and III volume administration is recommended with epinephrine titrated against the hemodynamic response. As second-line treatment, corticosteroids can be used, especially in asthmatic children early administration is beneficial. Although the role of intravenous steroids remains unclear, they may attenuate bronchospasm as well as angioedema. No evidence of optimal dose in anaphylactic shock exists. Recommended doses are similar to these in cases of severe asthma. In case of anaphylaxis with

Table 4
Second line treatment of anaphylactic reactions in children

Salbutamol/ipratropium
-Salbutamol:
- MDI: 4 puffs every 10 min if necessary,
- or nebulised 0.03 ml/kg/dose (up to 1 ml maximum), every 20-30 min
- 500 mcg (0.5 mg) of Ipratropium can be added
- Salbutamol IV: 5-25 μg/min

Anti H_1 (Histamine antagonist)
– Dexchlorpheniramine 0.15-0.3 mg/kg/dose slow IV or IM (maximum 5 mg)
– Clemastin 0.0125-0.025 mg/kg or
– Promethazin 0.3-1.0 mg/kg given IV/IM.
– Clorphenamine:
  - >12 years: 10 mg IM or IV slowly;
  - 6 to 12 years: 5 mg IM or IV slowly;
  - 6 months to 6 years: 2.5 mg IM or IV slowly;
  - < 6 months: 250 μg/kg IM or IV slowly.

Anti H_2 (H_2-receptor antagonist)
– Ranitidine 2-8 mg/kg diluted IV infusion in 20 min
– Diphenhydramine at doses of 25-50 mg or 0.5 to 2 mg/kg IV

Corticosteroids
– Methylprednisolone 2 mg/kg IV
– Hydrocortisone 10-15 mg/kg every 6 h or
  - > 12 years: 200 mg IM or IV slowly;
  - 6 to 12 years: 100 mg IM or IV slowly;
  - 6 months to 6 years: 50 mg IM or IV slowly;
  - < 6 months: 25 mg IM or IV slowly

predominance of respiratory symptoms, salbutamol is recommended (9). There is no clear evidence for H_1-or H_2-blocking drugs in children.

For children on β-blockers, with epinephrine refractory shock, glucagon can be administrated according to the hemodynamic state (starting at 20-30 μg/kg, with an infusion rate of 5-15 μg/min).

Premedication has been advised in the past but is proven not to be effective in preventing an immediate hypersensitivity reaction (20). Only frequency or intensity of non-IgE-mediated reactions can be reduced with pre-medication (12). Current opinion has moved away from this strategy (18).

Special precautions are advised regarding some allergies and pathologies. If previous perioperative reactions exist, the suspected drug should not be used and neither do products with possible cross-reactivity. In an emergency setting, regional anesthesia in a latex-free environment is advisable. In general anesthesia, volatile anesthetics are recommended, since allergy to these has not been reported (12). In case of latex sensitization is suspected, the patient must be referred for consultation before the operation (9). Patients sensitized to latex must be scheduled at the start

Table 5
Allergens during surgery

Antigen	**Incidence**	**Prophylaxis**	**Treatment**
Latex	< 4% in the general population Up to 76% in at-risk populations	- latex free environment - increased awareness - identification of latex allergy	Grade 2: - IV balanced salt solution (20 ml/kg 10-20 min) - Trendelenburg Grade 3: - Previous - Epinephrine 1-9 μg/kg, proportional to the severity Grade 4: - Previous - up to 10 μg/kg epinephrine - infusion of 0.1 μg/kg/min
Muscular relaxants	40-70%	- cross-reactivity testing	- Supportive therapy - Epinephrine - Corticosteroids - Antihistaminica? - Diagnosis of allergy - Tryptase levels - Allergic testing - Skin testing - Ig E - Histaflow/flow cytometry - Information and documentation
Antibiotics:	8-25%	- cross-reactivity testing	
Opioids	1.6% - 19%	/	
Colloids	0.033-14%	Cave gelatins and dextrans	
Local anesthetics	Rare	/	
Hypnotics	12%	Allergy to egg is no contraindication in the use of propofol	

of the operating schedule and in a latex-free environment (9,12). Systematically investigation before anesthesia is not necessary, except for patients at risk (9). This consultation is also for patients who had an unexplained reaction to an unidentified allergen during a previous operation, or patients who are known to be allergic to drug classes used during anesthesia (9).

In addition mastocytosis has to be ruled out in patients with a previous severe or atypical reactions during surgery and a negative allergological study. In case of confirmed mastocytosis, the use of tourniquets should be avoided because it may lead to the release of mediators by mast cells exposed to ischemia (12). Also special care should be provided to asthmatic children, who have a greater risk of bronchospasm during anesthesia. In case of anaphylaxis, this could be extremely severe. Avoidance of salbutamol 6h for anesthesia is advised if halogenated volatiles are used, in order to avoid the potential risk of arrhythmias or hypotension (12).

Desensitization is investigated for latex. Different methods are investigated (subcutaneous, percutaneous and sublingual), where sublingual desensitization is described to be clinically efficient and safe with compared to the subcutaneous and percutaneous route which leaded to adverse advents (17,18). It does not have an effect on serum level of specific IgE and high-risk group of children still require more efficient measures (18). The mechanism remains unknown and could not be explained by variation serum parameters nor immunological modulation (17).

Conclusion

Perioperative anaphylactic reactions are rare, but do known a high mortality and morbidity rate. The incidence of anaphylactic reactions is very depending on the geographic region with the relative exposure to allergens and the perioperative setting. A lower incidence is observed in children. Diagnosis of an anaphylactic reaction still contains some difficulties, partly to the low incidence, as well due to perioperative symptoms related to anesthesia which can be difficult to differentiate from allergic symptoms and partly because of the possible inconclusivity of testing. Histamine or MCT have a minimal role in pediatric population because of the special handling of the blood sampling of histamine and the rarely elevated titers of MCT in anaphylaxis with predominantly respiratory symptoms, typical for anaphylaxis in the pediatric subpopulation. Skin prick test remain the gold standard in detecting type I reactions, in addition they are less painful and thus more suitable for children. Use of basophil activation testing can bring an added value to skin testing and IgE tests, in the diagnosis of allergy. Despite development of testing, allergy to NMBA, latex and in particular opioids might be over-diagnosed. Primary treatment of allergy in children is similar as in adults with discontinuation of the allergen as one of the first steps, as well as notification of the team and the discontinuation of anesthesia, combined with symptomatic treatment (Tables 3,4,5). Due to the low incidence, difficulties in diagnosis, follow-up and reporting, clinical data around perioperative allergies in children remains limited. Providing a therapeutic suggestion, based on the available literature, can be helpful in institutions without a children based protocol. More investigation should be done in order to update the general guidelines regarding perioperative allergy in children.

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