

An update on allergy and anaphylaxis in pediatric anesthesia

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Abstract

Childhood allergy is common, and increasing. Many children are incorrectly labeled as having allergy or adverse drug reactions. This can pose a dilemma for anesthetists and lead to a change in practice or drug selection. We review the pathophysiology of hypersensitivity reactions and the implications for anesthesia of food allergy, atopy, and family history of allergy in children. The epidemiology of anaphylaxis is discussed. We discuss the common triggers of perioperative anaphylaxis in children and explore emerging triggers including chlorhexidine and sugammadex. Accurate data on pediatric perioperative anaphylaxis is limited worldwide, with marked geographic variation. This highlights the need for accurate local, district and/or nationwide incident reporting. The clinical features, diagnosis, and management of anaphylaxis under anesthesia are discussed. We review the process of expert allergy testing following a suspected case of anaphylaxis to guide future safe anesthesia administration. The preoperative consultation is an opportunity for referral for allergy testing to allow de-labeling. This has the potential for improved antibiotic stewardship and more effective treatment with first-line therapeutic agents.

KEYWORDS

allergy, anaphylaxis, outcome, pediatric anesthesia

1 | INTRODUCTION

Anesthetists are often confronted with a child with food allergy, atopy, a family history of allergy, or a child labeled as having an allergic reaction to a drug.¹ Epidemiological data suggest that the incidence of drug-induced anaphylaxis overall is increasing² highlighting the need for improvement in allergy reporting systems.¹ Allergy de-labeling is a growing area of research interest with a potential to improve patient care perioperatively.³ The common triggers, diagnosis, management, and follow-up testing of perioperative anaphylaxis are reviewed in this article. Concern over anaphylaxis risk has been shown to alter anesthetists' clinical practice⁴ and follow-up allergy testing is crucial to the diagnosis and prevention of further events.

2 | SEARCH METHOD

The databases Ovid Medline and PubMed were used. The following search terms were used: anesthesia, anaphylaxis, perioperative, pediatric, child, allergy, drug allergy, including articles published from 2005 to 2018.

3 | MECHANISM OF ALLERGIC REACTIONS

Allergic reactions are classified by Gell and Coombs, as summarized in Table 1. The term drug hypersensitivity reaction is often used in this context. Drug hypersensitivity reactions may be allergic or not

TABLE 1 Gell and Coomb's classification of hypersensitivity reactions adapted from source⁶⁵

Classification	Mechanism	Clinical presentation
Type 1- Immediate hypersensitivity reaction ^a	IgE antibody to specific antigens, mast cell stimulation, and release of inflammatory mediators	Wheeze, hay fever, eczema, food allergy, urticaria, laryngeal edema, angioedema, anaphylaxis
Type 2- Antibody-mediated cytotoxic reactions	Cytotoxic antibody: IgM, IgG bind specific antigens on cell membrane, complement activation, phagocytosis	Haemolytic transfusion reaction from ABO incompatibility, autoimmune hemolytic anemia
Type 3- Immune complex-mediated reactions	IgM and/or IgG Immune complex deposition in response to soluble antigen; complement activation	Serum sickness, vasculitis, glomerulonephritis, rheumatoid arthritis
Type 4- Delayed type hypersensitivity	Cell mediated by T-lymphocytes	Contact dermatitis, tubercular lesions, graft rejection
Other	Various	Nonspecific rash severe cutaneous adverse reactions (SCAR, eg, Stevens Johnson Syndrome, toxic epidermal necrolysis)

^aNon-IgE-mediated reactions mimicking Type 1 reactions may also occur, for example, direct histamine release caused by drugs for example, morphine, atracurium, vancomycin (red man syndrome)

allergic in nature with the term drug allergies being reserved for immunological-mediated hypersensitivities. For this review we use the term drug allergy throughout.

Allergic reactions are classified based on their pathophysiology where antibody mediated reactions characterize Type 1 to Type 3 reactions while Type 4 reactions are cell mediated (Table 1).

3.1 | Pathophysiology of anaphylaxis

Anaphylaxis is a systemic allergic reaction of sudden onset after exposure to an allergen, which manifests as life threatening compromise of the airway, respiratory, or circulatory function with or without dermatological findings.^{5,6}

Medications can trigger anaphylaxis through an IgE-dependent mechanism as well as direct mast cell activation. Following an initial sensitizing exposure, IgE antibodies are produced by B lymphocytes that bind to the high-affinity FcεRI receptors present on mast cells and basophils.⁵ Further drug exposure leads to the antigen-antibody complex inducing mast cell activation. There is release of preformed mediators including histamine, tryptase, heparin, and inflammatory mediators, such as cytokines like TNF-α, leukotrienes, prostaglandins leading to immediate allergic symptoms. This leads to recruitment and activation of additional inflammatory cells producing an amplified response over several hours.⁵

Some drugs can trigger anaphylaxis via direct mast cell or basophil activation, with no prior sensitization necessary. This has been identified with opioids, radiocontrast media, and some antibiotics such as vancomycin.⁶ Both triggering mechanisms can present the same way and are clinically indistinguishable.⁴

Sensitization does not always correlate with the presence of clinical allergy or anaphylaxis.⁷ The development of anaphylaxis following an exposure is influenced by immunological, hormonal, and environmental factors.⁸ To develop an allergy the patient has to have been exposed to the allergen before (knowingly or not knowingly). Previous tolerance of a medication does not predict lifelong tolerance as sensitization to a medication with regard to an IgE reaction can occur at any time.

4 | ALLERGY HISTORY TAKING

Children are frequently labeled as having multiple drug allergies without definitive testing.⁹ There is limited data for the prevalence of drug allergy labeling in children, however recent studies from Western Australia quoted a rate of 5%-7% at a tertiary pediatric centre.^{9,10} Up to 20% of adult inpatients are labeled as having antibiotic allergy,^{11,12} with only 10% of those patients having a true allergy.¹² Having an antibiotic allergy label is associated with inappropriate antibiotic prescribing¹¹ and increased hospital readmission compared to unlabeled patients.¹² Conversely, de-labeling of antibiotic allergies may reduce the use of broad spectrum antibiotics and prevent surgical site infections due to inadequate prophylactic cover from second-line agents.³

The anesthetist is met with the difficulties of parental recall of adverse drug events, preoperative time constraints, and limited institutional resources for allergy testing. Parents often mix up common drug side effects or intolerances as immune-mediated allergies.

Accurate allergy history taking and documentation is important to distinguish a true drug allergy from a simple adverse drug reaction. Immediate allergic reactions are usually present within 1 hour of exposure with the occurrence of urticaria, laryngeal edema, and bronchospasm and may lead to anaphylaxis.³ Non-IgE-mediated drug reactions may be delayed and present with maculopapular or morbilliform rash, gastrointestinal effects, headache, or pruritis.³ If clinical symptoms are suggestive of an immediate allergic reaction, the patient should be referred for allergic evaluation prior to the procedure if possible¹³ in relation to elective surgery and the causative agent should be avoided until further guidance by formal testing. Consensus recommendations from European and UK bodies recommend preoperative allergy testing for patients who have described a history of severe reaction consistent with anaphylaxis during previous anesthesia.⁴ The child with documented anaphylaxis to a medication should be referred for a MedicAlert bracelet to convey the risk if found unconscious or unaccompanied by an adult.

5 | COMMON ALLERGY-RELATED DISEASES IN CHILDHOOD

5.1 | Atopic disease

Atopic diseases include atopic dermatitis, food allergy, allergic rhinitis, and allergic asthma. Children with one of these illnesses are at a significant risk of developing another.¹⁴ The most basic underlying mechanism is the development of IgE antibodies directed against allergens that are usually harmless.¹⁴ Up to 40% of children progress from eczema to asthma and/or rhinoconjunctivitis, mostly before 5 years of age.¹⁴ A family history of atopic disease is a major risk factor.¹⁴ The propensity to atopy is hereditary, for example, if both parents have an atopic disease, this will also manifest in 40% of offspring.^{14,15} However, it is a common myth that specific drug allergies are hereditary; that is, if a mother is has anaphylaxis to a certain trigger the child will not necessarily be allergic to the same allergen (eg, penicillin).¹⁵

5.2 | Food allergy

Food is the leading cause of anaphylaxis overall in children.¹⁶ Common food allergy triggers are milk, eggs, peanuts, fish, soybeans, wheat, and tree nuts.¹ The prevalence of food allergy is greatest in the first years of life then falls in adulthood.¹ Longitudinal studies have found a resolution rate of 79% for milk,¹⁷ 68% for egg,¹⁸ 65% for wheat,¹⁹ 50% for soy²⁰ allergy compared to 20% for peanut²¹ and less than 10% for tree nut.²¹ Fish and shellfish allergy persist into adulthood.^{1,22}

Food allergies do not pose a contraindication to any anesthetic agents. There is no contraindication to propofol use in children allergic to egg, soy, or peanut.^{13,23} There is no cross reactivity between seafood or crustacean antigens and iodinated drugs such as povidone iodine and contrast agent,¹³ as although these agents all contain iodine, this is not the allergenic determinant.¹³ In addition, no allergic reactions to protamine have been reported in fish allergic patients.²⁴

6 | ANAPHYLAXIS

6.1 | Epidemiology

In the general population, the incidence of perioperative anaphylaxis is estimated as 1:10 000 in the recent UK-wide NAP 6 survey⁴ and Australian data.^{25,26} The true incidence of perioperative anaphylaxis is unclear as data are compiled from institution-based case series, administrative databases, or voluntary reporting systems in many countries²⁷ rather than formal reporting systems.

The incidence of perioperative anaphylaxis in the pediatric population is not comprehensively reported worldwide. The NAP 6 survey reported 11 cases of grade 3-4 anaphylaxis in pediatric anesthetics delivered, with an estimated incidence of 1:37 000,⁴ the 2017 APRICOT study reported an incidence of 1:10 000²⁸, and a French national database reported an incidence of 1:20 000.²⁹ Australian mortality data demonstrate a 300% increase in incidence and mortality from drug induced anaphylaxis from 1997 to 2005.²

It is important to note that anaphylaxis is the leading cause of "primary anaesthesia mortality" in Australia and New Zealand, and that all deaths occurred in adults.³⁰ One pediatric cardiac arrest and no deaths were reported in the French analysis,²⁹ and no deaths in NAP 6.⁴

6.2 | Risk factors

Several risk factors occur more frequently in children who develop perioperative anaphylaxis including a history of asthma, food allergy, multiple operations, and a family history of atopy.³¹ There is no sex difference in children, but the incidence of anaphylaxis is greater in adult females.²⁹ As the above factors are highly prevalent in the general population, they are not useful as screening tools.³²

The clinical features of anaphylaxis are shown in Table 2.²⁹ In children, severe anaphylaxis most commonly presents with bronchospasm or high airway pressure.⁴ "Resistant bronchospasm", that is refractory to initial epinephrine administration, is more common due to increased airway reactivity from underlying asthma and respiratory tract infections.³³

Grade	Symptoms
I (Mild)	Cutaneous signs: Generalised erythema, urticaria, peripheral angioedema
II (Moderate)	Measurable but not life-threatening symptoms: Cutaneous signs CVS: Hypotension, tachycardia Respiratory disturbance: cough, dyspnoea GI: difficulty swallowing, nausea, abdominal pain CNS: irritability, confusion, sense of impending doom
III (Life threatening)	Life threatening symptoms: Severe hypotension, tachycardia or bradycardia, arrhythmias Bronchospasm, high airway pressure
IV (Cardiac arrest)	Cardiac and/or respiratory arrest Most commonly presents as pulseless electrical activity

TABLE 2 Clinical grading of anaphylaxis adapted from Mertes et al³³

TABLE 3 Differential diagnoses for anaphylaxis under anesthesia adapted from ANZCA guideline³³

Symptoms	Differential diagnoses
Cutaneous signs: Hives, flushing, erythema, urticaria, angioedema	Direct histamine release Venous obstruction Head down position C1-esterase deficiency Mastocytosis Cold-induced anaphylaxis
Hypotension	Hypovolemia Peripheral vasodilation by drugs/ neuraxial blockade Sepsis Embolism: thrombotic, air, amniotic Vasovagal Cardiogenic shock
High airway pressure/ Respiratory compromise: Wheeze, stridor, dyspnea	Circuit malfunction Misplaced/kinked airway device Tension pneumothorax Asthma/Bronchospasm Airway foreign body Aspiration

TABLE 4 Triggers for perioperative anaphylaxis (adults and children) adapted from NAP 6⁴

Trigger	Percentage of cases with identified trigger agent
Antibiotics	46%
NMBAs	33%
Chlorhexidine	10%

Diagnosis of anaphylaxis under anesthesia is challenging for a number of reasons. Symptom onset is usually sudden and severe due to intravenous drug delivery. However, onset may be delayed from skin exposure to antiseptic or impregnated lines. As peripheral perfusion is reduced in shock, cutaneous features may be absent initially in more severe grades of anaphylaxis. Patients may be draped making the airway access and physical examination more difficult. The presenting symptoms are nonspecific with a broad list of differential diagnoses (Table 3). Anaphylaxis should be suspected in any case of patient deterioration under anesthesia especially if unresponsive to treatment.

Table 4 lists common triggers for perioperative anaphylaxis identified in NAP 6, however, this varies among countries.³⁴ Of the 11 pediatric cases identified in NAP 6, the trigger agents were atracurium in three cases, and one case each of suxamethonium, aprotinin, cefuroxime, and cryoprecipitate.⁴ Ibuprofen caused a nonallergic adverse reaction and no trigger was found in three cases.⁴ The findings above are in contrast to Mertes' study from 1997 to 2004 which identified latex, antibiotics, and

neuromuscular blocking drugs as the commonest perioperative anaphylaxis triggers in children. The adoption of a latex-free environment in many countries has drastically reduced sensitivity to and hence anaphylaxis to this trigger.³⁵

6.3 | Antibiotics

Antibiotic allergy is commonly reported in 5%-10% of children and may manifest as an immediate IgE-mediated (Type 1) or delayed T-cell-mediated (Type 4) reaction.¹⁰ However, this is complicated by the fact that 90% of patients are incorrectly labeled as having an antibiotic allergy.³⁶ This exposes patients to the risk of alternative agents, higher rates of surgical site infection, antibiotic resistance, nosocomial infection, and prolonged hospital stay.^{3,36}

Cephalosporins, followed by penicillins are commonly reported triggers of perioperative anaphylaxis in Europe³⁴ and Australia. Cephalosporins are commonly used in antibiotic prophylaxis, which poses a challenge for anesthetists. In general, cross reactivity between penicillin and cephalosporin allergy is rare, however, independent cephalosporin allergies can still occur.³ Penicillins and cephalosporins share a beta-lactam ring,³⁶ which is rapidly degraded and rarely antigenic.³ Potential cross reactivity is due to similarities of the R1 side chains attached to the beta-lactam ring.³ For example, cephazolin has a unique side chain structure and does not react with penicillins³, whereas ampicillin shares an R1 group side chain with cefaclor and cephalexin.³⁶ Severe T-cell-mediated delayed allergic reactions such as toxic epidermal necrolysis require referral for expert allergy consultation as cross reactivity between penicillins and cephalosporins may occur.³

Current recommendations by the American Academy of Allergy on cephalosporin use in the setting of proven penicillin allergy suggest that a convincing history of Ig-E mediated allergy should mandate formal allergy testing³⁷ and avoidance of the particular antibiotic class. Consensus opinion suggests that in adult patients without a history of severe reaction and no testing, cephalosporins may be given in a full dose or graded oral challenge.³⁸ These recommendations are debated and do not apply to the perioperative setting where an intravenous bolus dose of antibiotic is administered on induction of anesthesia. Data in the perioperative setting are limited to retrospective studies prone to selection bias and suggests very low incidence of anaphylaxis to cephazolin in penicillin allergic patients.³ Vorobeichik et al review this topic in detail.³

Of note, NAP 6 identified teicoplanin as the commonest anaphylaxis trigger,⁴ which illustrates geographical differences in sensitivity and local drug preferences. Vancomycin reaction under anesthesia is largely caused by nonimmune-mediated histamine release leading to "red man syndrome" if rapidly administered.

6.4 | Neuromuscular blocking drugs (NMBDs)

Neuromuscular blocking drugs are one of the most common causes of perioperative anaphylaxis in the general population with geographical regional differences with higher rates in Europe and Australia than observed in North America, implicated in 33%-58%

of reactions.^{4,34} The NAP 6 study found suxamethonium to have the highest rate of anaphylaxis per 100 000 administrations, followed by rocuronium and atracurium.³⁴ Patients who are allergic to one agent are likely to be cross reactive to other NMBDs.³⁹ Suxamethonium has the highest prevalence of cross-reactivity in patients allergic to rocuronium or vecuronium, whereas cisatracurium has the lowest.⁴⁰

A prior exposure to NMBDs or anesthesia is not required to develop allergy to a muscle relaxant. Epitopes containing a quaternary ammonium ion or tertiary amine group are common in drugs, foods, cosmetics, and industrial materials, raising the possibility of environmental exposure causing cross reactivity with NMBDs.³² Pholcodine is an over-the-counter antitussive drug available in Australia, which contains the quaternary ammonium ion epitope. Epidemiological studies have correlated pholcodine intake and the incidence of NMBA anaphylaxis. The drug was withdrawn in Norway in 2007, with a subsequent fall in perioperative anaphylaxis and IgE sensitization to pholcodine and suxamethonium.⁴¹ The immunological mechanisms behind these observations are still to be clarified.⁴²

The benzolisoquinolinium compounds (atracurium, mivacurium, cisatracurium) also cause direct mast cell histamine release which may present as a non-IgE-mediated anaphylaxis. A recent discovery of drug-receptor interactions between NMBDs and the "MRGPRX2" mast cell receptor has been postulated as a mechanism for nonallergic reactions to these drugs.⁴³

6.5 | Sugammadex

Sugammadex is a cyclodextrin compound used for reversal of steroidal neuromuscular blocking drugs such as rocuronium and vecuronium. Gamma-cyclodextrins are common food additives.⁴⁴ Sugammadex usage is highest in Japan, with an estimated incidence of anaphylaxis is 1:34 483.⁴⁴ The use of this drug is increasing worldwide, and its availability stimulates increased rocuronium use. Little is currently known about the mechanism of sugammadex-induced anaphylaxis due to the lack of sugammadex-specific IgE antibodies available for testing, and skin prick tests for the drug are still in development. Emerging case reports in the literature lacked previous exposure to sugammadex, suggesting cross-reactivity between sugammadex and another substance^{44,45} including a suspected case of anaphylaxis to the rocuronium- sugammadex complex.⁴⁶

6.6 | Chlorhexidine

Chlorhexidine is an emerging cause of allergic reactions, ranging from contact dermatitis to anaphylaxis.⁴⁷ Chlorhexidine applied to mucous membranes or skin may produce a delayed reaction, whereas insertion of a chlorhexidine-impregnated device can lead to a rapid and severe anaphylaxis.⁴ NAP 6 reported that diagnosis of chlorhexidine anaphylaxis was often not recognized, as it may not be obvious that certain products contained the allergen.⁴ If anaphylaxis to chlorhexidine is suspected, such indwelling devices should be removed and replaced with chlorhexidine- free alternatives if needed.⁴

6.7 | Propofol

Propofol is a rare cause of anaphylaxis under anesthesia, attributed to well below 1% of cases.^{4,29} The reported incidence of anaphylaxis to propofol is 1:60 000.⁴⁸ Potential allergens include (a) the propofol molecule itself via its isopropyl and phenol groups, (b) to the intralipid solution of glycerine, soybean oil, and egg lecithin or (c) preservatives such as disodium edetate (EDTA) or sodium metabisulfite.²³ There are a handful of case reports describing propofol allergy in children allergic to egg, soy, or peanut.⁴⁹ Egg allergic patients generally have immediate hypersensitivity to ovalbumin, a protein contained in egg whites, although lecithin is contained in the yolk. Moreover, most cases of egg allergy outgrow this with time.¹³ Thus, patients are unlikely to suffer anaphylaxis unless egg anaphylaxis is present. Peanut allergy is considered due to the potential uncommon (30%) cross-reactivity between peanut and soy.⁵⁰ The potential small amount of soy protein remaining in soy oil after the refining process is thought to be insufficient, even in a sensitized individual, to trigger a reaction¹³, however, no data exist on a threshold dose of contamination below which no allergic patient is likely to experience symptoms.⁵¹ A retrospective review did not find an association between food allergy and allergic reaction to propofol in children.⁵²

A retrospective review of egg, soy, and/or peanut allergic children who had received propofol found one child with anaphylaxis to egg who developed erythema and urticaria in the recovery room in 43 propofol exposures.⁴⁹ Other retrospective reviews of adult patients allergic to egg, soy, or peanut reported no allergic reactions on exposure to propofol.^{50,53}

6.8 | Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) induced anaphylaxis is most commonly due to a non-IgE mediated mechanism,⁵⁴ although immediate IgE and delayed T-cell reactions can occur.⁵⁵ NSAIDs inhibit cyclooxygenase, increasing production of leukotrienes which can manifest as bronchospasm, urticaria, and angioedema.⁵⁴ Subsequent skin tests are typically negative due to the lack of mast cell involvement. NSAIDs are implicated as a leading cause of drug-induced anaphylaxis in adults⁵⁶ and children^{55,57} outside the perioperative setting. Allergy testing is required to differentiate between specific allergy or cross-intolerance to all NSAIDs, and to suggest safe alternatives.⁵⁵

6.9 | Latex

Natural rubber latex is derived from the tropical *Hevea brasiliensis* tree and is widely used in the production of medical devices and everyday items. While many urethral and other catheters, sterile gloves, as well as products in the food and hairdressing industry used to be composed of latex in the past, many products have now been supplanted by nonlatex products. However, patients with a history of multiple surgeries, known latex sensitivity and atopy are still at

TABLE 5 Initial management of pediatric anaphylaxis under anesthesia, adapted from ANZCA Guidelines³³

Paediatric cardiac arrest	Manage according to advanced life saving guidelines:
	Start CPR
Recognition	Epinephrine 10 mcg/kg (0.1 mL/kg of 1:10 000)
	Crystalloid 20 mL/kg, repeat as needed (avoid gelofusion)
Airway	Unresponsive hypotension or bronchospasm
	Remove potential triggers for example, synthetic colloid, chlorhexidine, latex
Breathing	Stop procedure
	Use minimal volatile if general anesthesia
Circulation	Intubate early especially if:
	Airway edema
Epinephrine	CVS/ Respiratory compromise
	FiO2 100%
	Consider treatment of resistant bronchospasm:
	Inhaled salbutamol 100 mcg/puff (6 puffs < 6 y, 12 puffs > 6 y)
	IV salbutamol infusion per local protocols (eg 1-5 mcg/kg/min)
	Magnesium sulfate 50 mg/kg to max 2 g over 20 min
	Aminophylline 10 mg/kg over 1 h (max 500 mg)
	Hydrocortisone 2-4 mg/kg (max 200 mg)
	Rapid fluid bolus 20 mL/kg crystalloid, repeat as needed
	Plan for large volume resuscitation, obtain large bore IV access
	Initial IV Epinephrine Bolus (Pediatric)
	Dilution 1 mg in 50 mL = 20 mcg/mL
	Moderate anaphylaxis (Grade 2): 0.1 mL/kg that is, 2 mcg/kg
	Life threatening anaphylaxis (Grade 3): 0.2-0.5 mL/kg that is, 4-10 mcg/kg
	Give dose every 1-2 min prn, increase if unresponsive
	If no IV access
	IM Epinephrine (Pediatric)
	1:1000 1 mg/mL lateral thigh
	<6 y = 0.15 mL (150 mcg)
	6-12 y = 0.3 mL (300 mcg)
	>12 y = 0.5 mL (500 mcg)
	Every 5 min as required
	Pediatric epinephrine infusion
	1 mg Epinephrine in 50 mL (20 mcg/mL)
	Commence at 0.3 mL/kg/hr (0.1 mcg/kg/min)
	Titrate to max 6 mL/kg/hr (2 mcg/kg/min)

(Continues)

TABLE 5 (Continued)

Resistant hypotension	Consider norepinephrine and vasopressin infusion according to local pediatric protocol
	Consider isoprenaline and glucagon in beta-blocked patients
	Consider other differential diagnoses
After stabilization	Consider hydrocortisone 2-4 mg/kg (max 200 mg)
	Consider whether to proceed or postpone surgery
	Postoperative monitoring in intensive care/ high dependency unit

increased risk of anaphylaxis. Perioperative anaphylaxis to latex has markedly decreasing.³⁴

6.10 | Rare reactions

Anaphylaxis to intravenous gelatin containing colloids has an estimated incidence of 1:16 000,⁴ however, they are rarely used in children. Opioids, particularly morphine and pethidine may cause direct histamine release manifesting as pruritis, urticaria, and mild hypotension.⁵⁸

IgE-mediated anaphylaxis to benzodiazepines and local anesthetic agents are rare.

7 | MANAGEMENT

7.1 | Immediate

Early recognition, administration of epinephrine and fluid, and resuscitation are the mainstay of anaphylaxis management. The immediate management of anaphylaxis is summarized in Table 5. Children over the age of 12 are treated according to adult dosing. Following stabilization, patients should be observed in intensive care for 24 hours as anaphylaxis may persist or exhibit a biphasic response.

The Australia and New Zealand College of Anaesthetists anaphylaxis guidelines promote the use of cognitive aids in the form of a series of anaphylaxis cards to assist in crisis resource management. The cards are intended to be stored in an emergency "anaphylaxis box" in theatre along with information on local infusion protocols and collection tubes for tryptase testing. The anesthetist is the team leader directing theatre staff, with cards assigned to different team members to emphasize key tasks. Anaphylaxis drills should be practiced regularly to ensure familiarity with local guidelines and prompt management.⁴

7.2 | Diagnosis and follow-up testing

Mast cell tryptase (MCT) is a serum protease released from mast cells activated during an Ig-E mediated hypersensitivity reaction. There are two main types of MCT, alpha and beta MCT.⁵⁹ Alpha

pro-tryptase is constitutively secreted and is the major form of tryptase in serum, whereas beta tryptase is released rapidly in allergic reactions and elevated in most subjects with systemic anaphylaxis particularly in drug allergy.⁵⁹ Serum MCT is measured at 1 hour, 4 hours, and after 24 hours of the onset of anaphylaxis. The minimal elevation of the acute total tryptase level that is considered to be clinically significant is greater than $(2 + 1.2 \times \text{baseline tryptase levels})$, allowing detection of mast cell activation even when the tryptase remains in the normal range.⁶⁰ MCT can be elevated at baseline in rare conditions such as systemic mast cell disorders.⁶¹ It is important to note that a MCT within the normal range does not rule out anaphylaxis if there is a significant rise.⁵⁸

Following recovery, the patient is referred to a specialized perioperative allergy testing centre to investigate the reaction. The aim is to ascertain the trigger for anaphylaxis, cross reactivity with other anesthetic drugs, and formulation of a safe plan for suitable drugs for future anesthetics. Follow-up testing should occur 4–6 weeks after complete resolution of clinical symptoms to allow restoration of tissue mast cell granules.⁶²

The consultation includes the review of the nature and timing of the clinical reaction and all agents used intraoperatively as well as tryptase results. Skin prick and intradermal testing induce localized mast cell degranulation and a wheal and flare response which identifies IgE-mediated hypersensitivity.⁶³ International guidelines for perioperative allergy testing are published.^{63,64} Skin prick testing is highly sensitive for NMBDs but insensitive for antibiotics, barbiturates, benzodiazepines, and opiates.⁶² False positive results are possible if drug dilutions above the nonirritating concentration are used. If there is clinical suspicion of anaphylaxis but a negative skin prick test, intradermal testing is considered. Intradermal testing has a higher sensitivity and is performed routinely in Australasian centers. Skin tests will not detect the cause of non-IgE-mediated anaphylaxis⁶² but may yield false negative results.

Drug challenge testing can identify both allergic and nonallergic hypersensitivity. Drug challenge via graded oral, subcutaneous, or intravenous exposure may be required for critical drugs such as antibiotics, NSAIDs, opioids where skin testing is inaccurate, but the drug may be clinically needed in the future. It carries a risk of anaphylaxis and must be performed in a safe setting.³⁶

It is important to note that a drug with a high clinical suspicion of causing anaphylaxis but negative testing should be avoided.⁶²

8 | SUMMARY

Atopy, food allergy, and labels of specific drug allergy are common in children. There is a need for updated understanding of these issues for anesthetists. The preoperative assessment is an important public health opportunity to refer children with labels of drug allergy for testing.

Epidemiological data on perioperative anaphylaxis in children is limited, with marked geographical variation. There is a need for

systematic reporting of perioperative anaphylaxis to track local trends and inform prevention strategies. Neuromuscular blocking drugs and antibiotics are the most common triggers for anaphylaxis under anesthesia in children.

Children are more likely to present with resistant bronchospasm and less likely to develop cardiac arrest compared to adults. Timely recognition, removal of triggering agent, and administration of fluid and epinephrine are the mainstays of treatment. The use of cognitive aids and regular training will assist in the management of this crisis.

All patients with a suspected allergic reaction under anesthesia should be referred to a specialized anesthetic allergy testing centre for follow-up.

9 | REFLECTIVE QUESTIONS

1. What is the classification of allergic reactions?
2. What are common pediatric anaphylaxis triggers under anesthesia?
3. What are the local protocols for management of perioperative anaphylaxis in your institution? Are cognitive aids available, and if so, where are they located?
4. What are the reporting mechanisms for perioperative anaphylaxis and what are the processes for expert allergy testing in your institution?

CONFLICT OF INTEREST

The authors report no conflict of interest

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