



Pediatric Patients with Previous Anaphylactic Reactions to General Anesthesia: a Review of Literature, Case Report, and Anesthetic Considerations

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Abstract

Purpose of Review It is rare to see pediatric patients with previous perioperative anaphylaxis receiving future anesthesia, but it is critical to understand how to choose assessments, interpret the results, and develop a future anesthetic plan.

Recent Findings Analysis of the results revealed that patients, at any age, regardless of sex and nationality, and the number of surgeries, have the risk of perioperative anaphylaxis while the risk of allergy increases as patients present multiple surgical events or have a previous history of atopy. 94.7% of pediatric patients with allergy testing after perioperative anaphylaxis tolerated subsequent general anesthesia without complications. Specific IgE tests, basophil activation tests, and skin tests are not available and suitable for all culprits. The early skin test could be considered a supplement for later testing. Drug challenge test is the golden standard but can only be used as the last resort. If general anesthesia is inevitable, avoidance of the culprit and use of alternative agents can help the patients prevent another potential recurrence. Full use of inhalation anesthesia without unnecessary neuromuscular blockade agents and avoidance of latex is recommended when the surgery is urgent or skin tests for children cannot be performed in time.

Summary This review summarizes characteristics of perioperative pediatric anaphylaxis, main tests for various drugs, and their sensitivities and specificities as well as recommendations as to how to implement safe anesthesia in the future.

Keywords Pediatric patients · Anaphylaxis · Anesthesia · Skin test · Neuromuscular block agents

Introduction

Anaphylaxis is defined as a severe, rapid onset, potentially lethal, systemic hypersensitivity reaction [1], and perioperative

anaphylaxis refers to anaphylaxis caused by agents used in perioperative period, not exclusively attributed to anesthesia. The exact incidence of anaphylaxis during anesthesia varies from different regions and lacks accuracy. It has been estimated between 1 in 1250 and 18,600, and perioperative anaphylaxis contributes to 0~9% of anesthesia-related deaths based on several studies [2, 3]. Statistical data on perioperative anaphylaxis in pediatric patients are scarce. The overall incidence in children is a little less frequent to that reported in adults; the NAP 6 survey reported that the incidence of perioperative anaphylaxis is 1:10,600 in pediatric patients, with an estimated incidence of 1:37,000 in grade 3–4 anaphylaxis [4]. It occurs at less than 5% of patients aged 10 years or younger and less than 10% of patients aged between 10 and 18 years [5, 6]. However, anesthesiologists encounter the situation in which pediatric patients with previous perioperative anaphylaxis would receive surgeries again, and anesthesiologists are required to develop appropriate anesthesia plans to prevent an anaphylactic reaction from recurring. The incidence of perioperative anaphylaxis is low, and it is rare to find pediatric patients with a history of perioperative anaphylaxis receiving future anesthesia in our hospital.

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Thus, a literature search was performed to summarize the information related to assessment methods and results and to give suggestions as to how to implement safe anesthesia in the future. Then, we also presented a case report that a 22-month-old girl who had experienced two episodes of perioperative anaphylactic reactions was anesthetized successfully. We shared our experience on the evaluation of pediatric patients who cannot cooperate with skin tests.

Methods

A literature search was carried out in electronic databases such as PubMed, Medline, and VIP database for Chinese Technical Periodicals, Wanfang database, and China National Knowledge Internet using the keywords: (anaphylactic reactions OR anaphylaxis OR allergy) AND (general anesthesia OR intraoperative OR perioperative). The latter three databases are well known in China and frequently used in research studies. They cover all articles published in Chinese. We included articles published only in English and Chinese. The search was conducted from January 1998 to December 2017.

Two authors (MMJ and LHY) independently screened the titles and abstracts of all the articles obtained by the initial search. Complete manuscripts were evaluated if articles were considered necessary to be reviewed in full. These authors independently assessed full texts using a set of eligibility criteria as follows: (1) pediatric patients (< 18 years old) were reported; (2) the study was a primary investigation or case report in which a patient had anaphylaxis when receiving previous general anesthesia (GA) and received surgeries again; and (3) the study gave a description of suspicious drugs or items, anaphylactic reactions, investigations, and strategies for the subsequent anesthesia. The patients were excluded if (1) they were adults; (2) they were allergic to transfusion or blood products; (3) they suffered mastocytosis, mast cell diseases, angioedema, or liver hydatid cyst; and (4) they showed symptoms of anaphylaxis more than 24 h after being anesthetized. A figure is drawn for the selection process (Fig. 1).

The same authors independently performed data extraction from each case using a prestructured table, specifically designed for this review. The table included general information such as the country where a case was reported with the title and authors of the study. Details of case reports were also collected, including the patient's age, sex, weight, a history of allergy and atopy, the number of previous operations performed, medications used during induction as well as maintenance, descriptions of anaphylactic reactions, treatments given for those reactions, information as to the previous anaphylaxis grade [7], tests to determine culprit and their results, types of the subsequent surgeries (elective, limited, or urgent), strategies for the next anesthesia, and prognosis. Any discrepancy between two reviewers about articles se-

reened and information extracted was further discussed and solved by consensus after a secondary review of the original articles under the guidance of another author (ZB).

Results

The database search yielded a total of 795 publications. Title/abstract screening excluded 566 articles. Out of the 229 articles, 211 failed to meet the eligibility criteria due to adult-only articles or not containing repeat anesthesia information. We identified a total of 18 studies (21 cases) to be included: two patients in three case series and fifteen case reports. Table 1 summarizes patient demography and previous anesthesia information of all included cases. Among these patients, the first case experienced an anaphylactoid reaction with all tests negative. The age of included patients had a wide range with a minimum of 4.3 months. The proportion of male to female was roughly the same. Patients younger than 10 years old constituted 33.3%. Except Africa, countries in five continents have reported anaphylactic cases. Eight cases (38.1%) had a previous history of allergy or atopy. One case of perioperative anaphylaxis occurred before anesthesia was given, five cases (23.8%) occurred during induction, fourteen cases (66.7%) occurred in the maintenance phase, and one case occurred postoperatively. The grade of the anaphylactic reaction was grade II in five cases (23.8%), grade III in thirteen cases (61.9%), and grade IV in three cases (14.3%).

Table 2 summarizes the tests to determine the culprit drugs or items. Eleven cases (52.3%) received skin tests, one case measured the level of histamine, six cases measured the serum level of tryptase, ten cases measured the specific immunoglobulin E (sIgE), and two cases did not receive any test. The culprits were muscle relaxants in four cases, fentanyl and methylprednisone in one case, latex in seven cases, gelatin in topical hemostatic materials in two cases, ethylene oxide (EO) in one case, and uncertain sources identified in six cases. Additionally, two cases that were known to have latex allergies preoperatively adopted latex-free precautions.

Table 3 summarizes the strategies for repeat anesthesia and prognosis. The seventeenth case included in the table was shifted to local anesthesia after being confirmed not allergic to local anesthetics. Eighteen of the nineteen patients (94.7%) with allergy testing after perioperative anaphylaxis tolerated subsequent GA without complications. The sixteenth patient was identified to be allergic to EO, which, however, can only be reduced but not be eliminated. This patient suffered the grade II anaphylaxis during the subsequent GA but underwent the planned surgery successfully. One case of the two patients who did not receive any test had not been realized it was an allergic reaction and then it recurred. The other case adopted

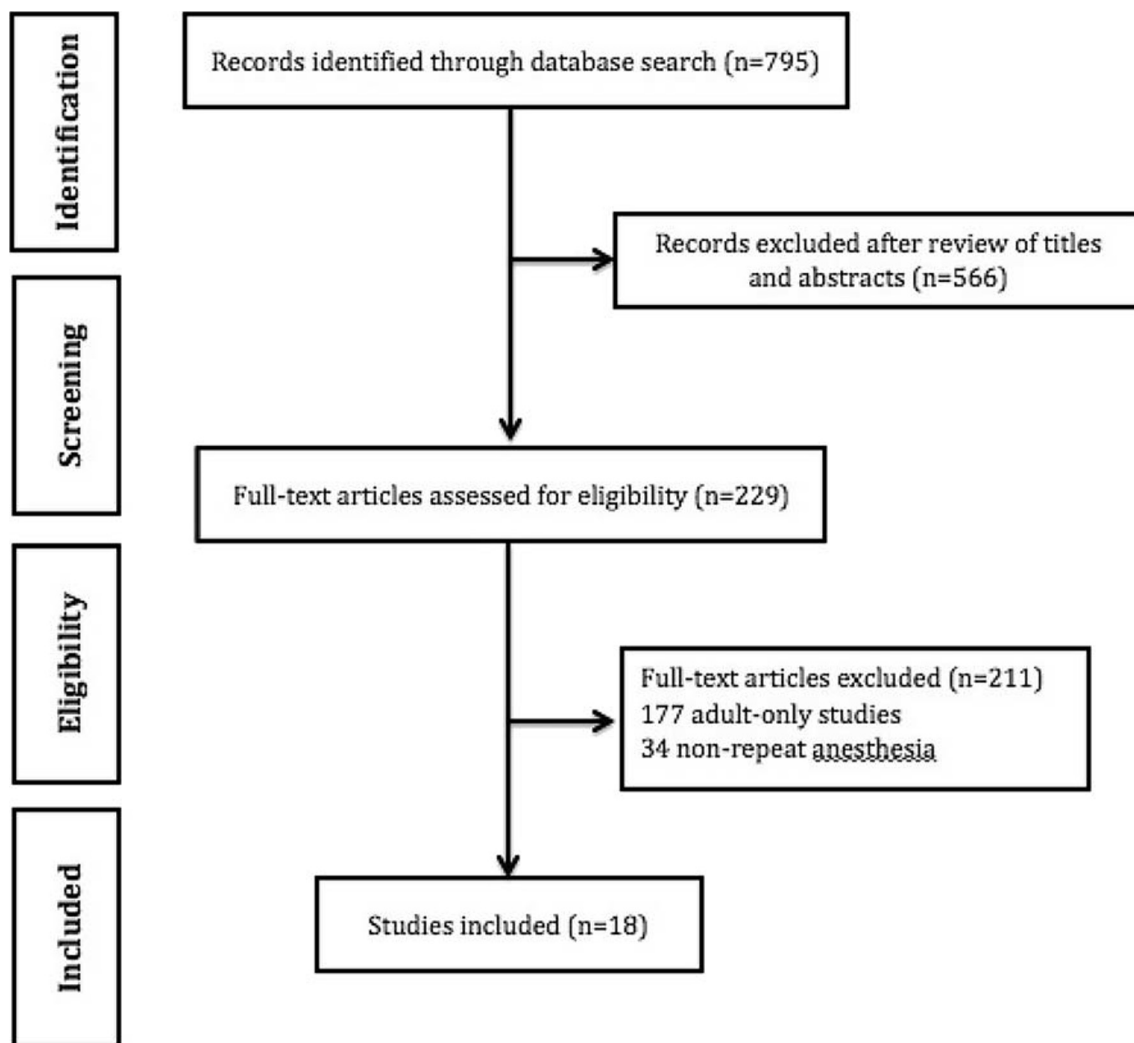


Fig. 1 Flowchart of the retrieved, excluded, and analyzed case reports

latex-free protocol by asking medical history and underwent a successful surgery.

Case Report

The above literature search yielded no results with relevance to the management for the skin test process. Therefore, we included a case we encountered and shared our experience on the evaluation of pediatric patients who cannot cooperate with skin tests.

A 22-month-old girl (height 85 cm, weight 11 kg) was scheduled for cleft lip and palate repair. However, she had experienced two episodes of suspected anaphylactic reactions during anesthesia when she was 10 months old and 20 months old, respectively. According to the anesthetic record, the first suspected anaphylaxis occurred within 1 min after she was induced with propofol, sufentanil, cisatracurium, and ondansetron. The clinical manifestations of suspected

anaphylaxis included hypotension associated with tachycardia, high peak airway pressure, and generalized rashes. She was resuscitated with epinephrine and transferred to PICU. As a result, the surgery had to be deferred and the patient's safety was subsequently secured. The patient had no recent upper respiratory infection, asthma, or a documented allergy history. However, a small dose of propofol produced the second suspected anaphylaxis in which blood pressure abruptly dropped to 30 mmHg when the anesthesia was induced. The blood pressure restored to normal with the use of epinephrine, but the surgery was canceled again.

Under the informed written consent, 8 weeks after the last anesthesia, the little girl was arranged to receive the intradermal tests (IDT) and basophil activation tests (BAT) to the suspicious drugs. Preparations for the tests included the following: strict fasting time, sedative drugs, monitoring, self-checked anesthesia apparatus, intubation-related tools, and emergency drugs. Given that she could not cooperate with so many tests quietly, she was sedated with an intramuscular

Table 1 Tabular summary of case report—patient demographics and previous anesthesia

Pt	Country	Sex/age ^a	History of surgery	Allergic or atopic history	Stage: suspicious drugs/items	Anaphylaxis grade
1 [8]	USA	M/4.5 months	0	No	Maintenance: methylene blue	III
2 [9]	KOR	F/33 months	0	No	Induction: propofol, rocuronium	III
3 [10]	KOR	F/3 years	0	No	Induction: rocuronium	II
4 [11]	CHN	F/6 years	0	Yes	Induction: cisatracurium	IV
5 [12]	ITA	M/8 years	4	No	Maintenance	IV
6 [13]	AUS	F/8 years	4	Yes	Maintenance	III
7 [14]	USA	M/9 years	2	No	Maintenance	II
8 [15]	USA	F/10 years	0	No	Maintenance: gelfoam	III
9 [16]	Serbia	M/11 years	2	No	Maintenance: fentanyl	III
10 [17]	BRA	F/11 years	1	No	Postoperative	II
11 [18]	USA	F/12 years	1	Yes	Maintenance: floseal	III
12 [13]	AUS	F/13 years	16	No	Maintenance	III
13 [18]	USA	M/13 years	0	Yes	Maintenance: floseal	II
14 [14]	USA	M/13 years	M ^b	No	Maintenance: a red rubber	II
15 [19]	USA	M/13 years	3	Yes	Maintenance	III
16 [20]	CHE	M/13 years	M	Yes	Maintenance	III
17 [21]	CHN	M/14 years	0	Yes	Preoperative	III
18 [22]	USA	M/14 years	M	Yes	Maintenance: gelfoam, floseal	III
19 [23]	GBR	M/15 years	0	No	Maintenance: atrial catheter	IV
20 [24]	USA	F/17 years	0	No	Induction: rocuronium	III
21 [25]	AUS	F/17 years	1	No	Induction: rocuronium	III

USA United States of America, KOR Korea, CHN China, ITA Italy, AUS Australia, BRA Brazil, CHE Switzerland, GBR United Kingdom

^a Age at the reaction

^b Multiple surgeries

injection of ketamine 60 mg in the operating room. Then, 2 ml of blood was drawn for BAT, and venous access was established after the girl fell asleep with spontaneous breathing preserved during the entire test. The deep sedation was maintained with sevoflurane and intermittent intravenous administration of ketamine (15 mg in total). It took about 1 h to complete the skin test uneventfully. Afterward, the girl was transferred to PACU. The results demonstrated positive IDT to cisatracurium and ondansetron, but negative BAT to all of the test drugs. Given the anaphylactic reaction to propofol in the second anesthetic induction, the use of cisatracurium, ondansetron, and propofol must be avoided in the future anesthesia.

On the day of surgery, she was fully monitored and was induced with sevoflurane. After venous access was established, fentanyl 20 µg and methylprednisolone 20 mg were given intravenously, and a 4.0# endotracheal tube was intubated successfully, followed by mechanical ventilation. The anesthesia was maintained with inhalational sevoflurane (2%) and nitrous oxide (60%), intravenous infusion of remifentanyl (50 µg/h), and intermittent intravenous injection of fentanyl (total dose: 60 µg) without any use of muscle relaxants. The surgery and anesthesia proceeded uneventfully. She was extubated and transferred to PACU after the surgery.

Afterward, she received three more surgeries successfully with similar anesthesia strategies.

Discussion

As far as we know, this is the first systematic review of literature related to the management of pediatric patients with previous anaphylactic reactions to general anesthesia. Our review identifies a few critical findings. Firstly, patients, at any age, regardless of sex and nationality, have the risk of perioperative anaphylaxis. It has been widely accepted that the risk of anaphylaxis to drugs is lower in children who possibly possess the immature immune systems [26]. In adults, the most common causative agents of perioperative anaphylaxis include antibiotics (47.2%), muscle relaxants (32.7%), and chlorhexidine (9.0%) reported in the NAP 6 survey [2]. However, in the group of children under 18 years in France, latex (41.8%) is the most frequent cause, followed by neuromuscular blockade agents (NMBAs) (31.97%) [27]. The incidence of latex allergy is decreasing at present due to the strict avoidance of latex-containing products [28**]. Anaphylaxis to gelatin, ethylene oxide, and other antiseptics has attracted

Table 2 Tabular summary of case report—tests to determine the culprit

Pt	Skin test	Tryptase	Specific IgE	Culprits
1	6 weeks later, dye (–)	(–)	ND	Undetermined, dye in suspicious
2	ND	ND	ND	Undetermined
3	4 weeks/3months, rocuronium (+)	ND	ND	Rocuronium
4	1 week, cisatracurium(+)	ND	ND	Cisatracurium
5	1 week, NMBAs (–)	ND	Latex (+)	Latex
6	ND	ND	Latex (+)	Latex
7	ND	ND	Latex (+)	Latex
8	ND	(+)	Gelatin (+)	Gelfoam
9	6 weeks, (+)	ND	ND	Fentanyl and methylprednisolone
10	6 years, resin-epoxy (+)	ND	ND	Latex
11	ND	(–)	Gelatin (+)	Undetermined, floseal in suspicious
12	ND	ND	Latex (+)	Latex
13	ND	(+)	Latex, gelatin(–)	Undetermined, floseal in suspicious
14	ND	ND	Latex (+)	Latex
15	ND	ND	ND	Undetermined, latex in suspicious
16	EO (+)	ND	EO (+)	EO
17	6 months, lidocaine(–)	ND	ND	Undetermined
18	4 weeks, gelatin (+)	(+)	ND	Gelfoam
19	ND	(+)	Latex (+)	Latex
20	6 weeks, rocuronium (+)	ND	ND	Rocuronium
21	1 day/10 weeks, rocuronium (+)	ND	ND	Rocuronium

Abbreviations: EO ethylene oxide, NMBA neuromuscular blocker agent, ND no data

Table 3 Tabular summary of case report—strategy and prognosis

Pt	Urgent surgery	Strategy for the next anesthesia	Prognosis
1	No	Use an alternative marker, avoid morphine	Uneventfully
2	No	No awareness	Recurrent anaphylaxis
3	Limited	Avoid muscle relaxants	Uneventfully
4	Limited	Use alternative vecuronium, avoid protamine after CPB	Uneventfully
5	No	Latex-free protocol	Uneventfully
6	No	Latex precautions	Uneventfully
7	No	Latex-safe conditions	Uneventfully
8	No	Avoid gelatine	Uneventfully
9	No	No fentanyl, use a continuous infusion of remifentanyl	Uneventfully
10	No	Latex-free protocol	Uneventfully
11	No	Avoid rocuronium and floseal	Uneventfully
12	No	Latex precautions	Uneventfully
13	No	Avoid rocuronium, albumin, and floseal	Uneventfully
14	No	Latex-safe precautions	Uneventfully
15	No	Latex-free protocol	Uneventfully
16	No	Latex-free and reduction of EO level	Grade II anaphylaxis
17	No	Swift to local anesthesia	Uneventfully
18	No	Avoid gelatin products, latex, and cephalosporin	Uneventfully
19	No	Latex-free technique	Uneventfully
20	No	Avoid rocuronium, use cisatracurium	Uneventfully
21	Limited	Avoid muscle relaxants, maintained with sevoflurane	Uneventfully

Abbreviations: CPB cardiopulmonary bypass, EO ethylene oxide

much attention. In adults, a female to male ratio of perioperative anaphylaxis is 3:1 [5], while there is no disparity between boys and girls in perioperative anaphylaxis [27]. The inciting agents differ in different regions. The estimated incidence associated with muscle relaxants during the perioperative period ranges for a large scale [24], and it is much lower in the USA compared with other countries [29] because pholcodine is available in many European countries but not in the USA.

Anaphylaxis is common in patients without known previous exposure to any anesthetics, particularly NMBAAs [30]. The possible explanation to it is that the daily-use products share the same allergenic epitopes, probably quaternary ammonium ions, with NMBAAs [31]. In addition, the risk of latex allergy increases as patients have multiple surgeries, and two operations are enough to cause sensitization in high-risk patients such as children with spina bifida [32]. Patients with a previous history of atopy have a higher risk of allergy to latex and propofol [29]. In this review, nine cases except one with latex allergy had a previous history of surgery and even multiple surgeries.

Once patients experience suspected perioperative anaphylaxis, all of them are at increased risk of anaphylaxis recurrence [33] and should be referred to an allergic assessment [30]. This referral is performed to confirm that the adverse perioperative event was anaphylaxis, to determine its responsible agent, and to recommend alternative agents. In one adult study, ten patients underwent further surgeries successfully after confirming the culprit drugs and identifying alternative drugs by investigating the clinical history and medical records, results of laboratory tests and skin tests [34]. The main tests for various drugs and their sensitivities, specificities, and recommendations are listed in Table 4.

The serum level of histamine has a limited role in the pediatric population because of short half-life and special handling of blood sampling. A few guidelines highlight the importance of serum tryptase measurement [41]. Tryptase released only by activated mast cells allows more reliable testing and is possibly measured in blood samples drawn for other purposes, but a normal level does not exclude anaphylaxis because its reported sensitivity is 64% and the specificity is 89% [42]. If the serum tryptase is elevated, it is recommended performing a repeat measurement after the patient has recovered to assure it is not persistently elevated to exclude systemic mastocytosis and mast cell diseases. Two of the four patients with elevated tryptase levels performed a repeat measurement and showed a normal level in this review. Serum sIgE is not consumed after the anaphylaxis occurred for a long time. When an early reintervention, shorter than 4 weeks, is necessary, sIgE determination can contribute to identifying the culprit drugs [43]. However, sIgE tests for a few drugs are still not available in many countries. It is reported that one third of

spina bifida patients with latex allergy are sensitized against EO. The cases with recurrence of anaphylaxis in a latex-free environment could potentially have been due to EO, and thus, the scale of the problem is likely to be underestimated [44].

Skin tests are the golden standard for the diagnosis of IgE-mediated allergic reactions [45]. The sensitivity of skin tests can reach up to 97% in NMBAAs [46], but poor sensitivity exists for benzodiazepines. That is possibly why propofol with negative skin test result caused the second anaphylactic reaction in our case. Due to the common cross-reactivity between NMBAAs [47], skin tests should involve all available NMBAAs and only the ones with negative results can be re-used in the future [48]. The guideline recommends that skin tests be carried out 4–6 weeks after the anaphylaxis in order to avoid a false-negative test result [35^{**}]. However, guidelines also recommend referring the patient for skin tests as soon as the patient has recovered [30], or even immediately after a reaction in an emergency situation [49]. Early skin tests could be considered a supplement for later testing, and only positive results should be taken into account [50]. One study reported the agreement rate among early skin tests and standard skin tests was 70.45%, and three of the 25 patients with positive results in early skin tests were negative at standard skin tests [51]. In this review, three of the ten patients with skin test results underwent early skin tests due to limited surgeries, but only one of them was reexamined with standard skin tests. When skin tests for propofol or opioids in high suspicious of anaphylaxis yield negative results, a drug challenge test (DCT) can give a definitive diagnosis and better safety in later surgery with balance of risks and benefits [52^{**}]. However, studies of DCT in pediatric patients have not been performed as far as we know.

All studies included no BAT except our case. The BAT might constitute a promising and useful tool to confirm the diagnosis of perioperative anaphylactic reactions and identify a safe alternative, particularly for NMBA-induced anaphylaxis. It affirms that when one of NMBAAs yields both negative skin test and negative BAT results, patients can safely be administered this type of NMBAAs during future anesthesia [53]. The BAT for NMBAAs in our hospital attains a sensitivity of 42.9% and a specificity of 97.2% [36]. The sensitivity of BAT varies and remains unclear, so it has not become a widely used technique in daily clinical practice [36].

In reality, the assessment cannot be routinely performed in every hospital in many countries. Most anesthesiologists carry out the subsequent anesthesia based on their experience. A retrospective survey reported that the most frequently suspected substances as culprits were opioids, antibiotics, and NMBAAs, while the overlooked allergies were latex, chlorhexidine, low molecular weight heparins, and local anesthetics [54]. A meticulous analysis of previous suspected anaphylactic reaction must be undertaken based on temporal relationship because 90% of reactions occur during induction or within

Table 4 Main tests for various drugs and their sensitivities, specificities, and recommendation

Drug	Main tests	Sensitivity	Specificity	Recommendations	Reference [35**]
Latex	Specific IgE	63–94%, medium to high	100%, High	Yes	[12]
	Skin test	> 90%, high, only SPT, trigger test	> 90%, High	High risks, not recommended	[12]
NMBA	Skin test	94–97%, high	High	Yes, including cross-sensitivity	[10]
	BAT	63–89.7%, medium to high	High	Combined with ST or when ST cannot be done	[36]
Antibiotics- β -lactams	Specific IgE	Only suxamethonium is available, 30–60%, low	ND	Not available and not recommended	[37]
	Skin test	About 50%, medium	97–99%, high	Yes	[38]
	Specific IgE	Low	ND/may be high	When ST is negative but highly suspicious	[38]
	BAT	40–50%, medium	80–100%, high	Not validated and not recommended	[39]
Propofol	Skin test	ND/poor	ND/not very high	Can be done	[35**]
Opioids	Skin test	ND/poor	ND/not very high	Can be done	[16]
Dye	Skin test	ND/may be high	ND/may be high	Yes, including cross-sensitivity	[8]
Gelatin	Specific IgE	ND/may be high	ND/may be high	Can be done if it is available	[18]
	Skin test	ND/may be high	ND/may be high	Yes	
Ethylene oxide	Specific IgE	ND/may be high	ND/may be high	Yes	[20, 40]
	Skin test	ND/may be high	ND/may be high	Yes	[20, 40]
	BAT	ND	ND	Not validated and not recommended	[40]

Abbreviations: SPT skin prick test, ST skin test, BAT basophil activation test, NMBA neuromuscular blocker agent, ND no data

minutes following intravenous injection of the offending agents as with NMBA, antibiotics, or propofol. If signs appear during the maintenance phase, it often suggests an allergy to latex, volume expanders, topical hemostatic material, or dyes [45]. It should be noted that there was a gap between administration and onset. For example, there is a 15-min gap between the administration of fentanyl and the anaphylactic reaction [16]. The reaction to latex is often delayed, up to 60 minutes, but an early onset does not exclude latex allergy because the anaphylactic reaction to latex can be caused through not only type I but also type IV immediate hypersensitivity reactions. In this review, an anaphylactic reaction occurred after the patient left the hospital and later was identified as latex allergy (the tenth case). If the evaluation is not available, general measures for patients requiring repeat anesthesia include using a different anesthetic technique if possible such as local, regional, or inhalational anesthesia, avoiding latex and muscle relaxation, or switching to another type of antibiotic and antiseptic [25]. Although one study reported 15 of the 19 patients had previously been allergic to the aminosteroid (e.g., rocuronium) and were subsequently uneventfully exposed to a benzylisoquinoline such as atracurium or cisatracurium [53], there were patients allergic to both an aminosteroid and a benzylisoquinoline [55]. It should always be borne in mind that not identifying the culprit agent necessitates the use of multiple second-line agents that are not without risk to patients.

In our case, the obstacle was that the girl was too young to cooperate with us. The sedative plan and even the choice of emergency intubation drugs required a comprehensive consideration. The guideline recommends that it should be appropriate to avoid all medications used during the previous anesthetic before the onset of cardiorespiratory collapse except for inhalational agents [30]. Propofol is responsible for less than 2% of anaphylactic reactions, but only a small dose of propofol in the second anesthetic induction led to the severe anaphylactic reaction, so propofol should be avoided. Concerning ketamine, its related anaphylactic reactions remain extremely rare, and no reactions to inhaled volatile anesthetics have been described so far [30, 33]. These two kinds of anesthetics seemed to be the best choices. We informed the child's parents of the risks and got sufficiently prepared for the skin tests due to high risks. This girl was further performed cleft palate repair under general anesthesia twice using the same strategies, which was well documented in the anesthesia sheet for the safety of subsequent procedures [56]. However, little information can be obtained about cooperation with skin tests from infant and toddler cases (age younger than 3 years old) included in this review.

Although there is no evidence that pretreatment with hydrocortisone is useful in preventing anaphylaxis [13], premedication efficiently reduces the frequency or intensity of non-IgE-mediated reactions [22]. In this review, two case

reports (the fifth and the ninth case) documented that the patients received pretreatment with hydrocortisone in the future anesthesia. The ninth patient [34] received methylprednisolone, but he developed bronchospasm again, so anesthesiologists should weigh the advantages and disadvantages when considering using it as a preventive agent.

Our review has several limitations. First, we are limited to draw quantitative conclusions based solely on an analysis of case reports. The prognosis of most cases included in this review was satisfying because doctors tend to report successful cases. Second, there is limited descriptive data about the patients included in the studies. Specific IgE tests, basophil activation tests, and skin tests are not available and suitable for all culprits. We cannot even analyze the results of skin tests deeply.

In conclusion, although perioperative anaphylactic reactions rarely occur, they can happen in any patient at any time, and we should always get ready for fighting the devastating complication. Once it occurs, patients should be extensively investigated, including a careful review of their history (atopy and surgery) and medical records, and a proper assessment of timing and techniques on a wide range of agents to identify culprits and alternative agents. Generally speaking, if GA is inevitable, avoidance of the culprit and use of alternative agents, especially NMBAs with negative results in skin tests, may help the patient prevent another potential recurrence. Full use of inhalation anesthesia without unnecessary NMBAs and avoidance of latex is recommended if surgery is urgent or skin tests for children cannot be performed in time. Not identifying the culprit agent necessitates the use of multiple second-line agents that are not without risk to patients, and the best insurance of safe subsequent anesthesia is a well-documented safe anesthetic record.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent Approval was obtained from the ethics committee of Peking Union Medical College Hospital. The procedures used in case report adhere to the tenets of the Declaration of Helsinki.

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