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Review

Perioperative anaphylaxis: A new visit to an old topic

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Contents

1. Introduction

The term anaphylaxis is quite an old term, being first described by Portier and Richet in 1902 [1], derived from the Greek word “phylax”, meaning “to guard”; anaphylaxis means “loss of guard or

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protection".

Anaphylaxis is a severe life-threatening, generally unanticipated, allergic reaction, often with explosive onset, resulting in a clinical syndrome affecting multiple organs. The latest International Consensus on Anaphylaxis (ICON) defines anaphylaxis as "a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal" [2]. These reactions should be differentiated from those caused by pharmacologic idiosyncrasy, by direct toxicity, drug overdose, or by drug interactions [3]. The majority of anaphylactic reactions occur in the community, but more than a third of all patients admitted to intensive care with severe anaphylaxis come from operating theatres [4].

The classification of anaphylactic reactions looks confusing at some point, especially with the introduction of the term "anaphylactoid" to describe non-immune anaphylaxis-like syndrome, which involves more or less the same pathway and cells but without the involvement of immunoglobulin E (IgE) as a trigger. To resolve this conflict, the European Academy of Allergy and Immunology (EAACI) nomenclature task force [5] has suggested that anaphylactic reactions should be reclassified into allergic anaphylaxis and nonallergic anaphylaxis, the latter being the "anaphylactoid reactions", and the allergic anaphylaxis being further classified into IgE-mediated and non-IgE-mediated reactions.

Delivering anesthesia involves injecting not only hypnotics and analgesics, but also antibiotics, steroids, NSAIDs and several others (average of eight drugs, but the number can be as high as 20 [6]). Intravenous injection exposes mast cells and basophils to a huge amount of antigens suddenly, which in turn is translated into this massive expression and degranulation [7].

Anaphylaxis, therefore, should be always kept a differential diagnosis in a collapsing patient, to recognize it early and work promptly to improve the outcome and reduce morbidity and mortality.

In this review we are trying to cast light on the updates about perioperative anaphylaxis, by reviewing the topic from different aspects; pathophysiology, epidemiology, causative agents and management options.

2. Epidemiology

The incidence of peri-operative anaphylaxis is quite rare depending on different estimates, which reflect differences in clinical practice and reporting systems [8]. It ranges between 27.9 in 10000 (grade I) and 7 in 10000 (grade II, III and IV) in a Brazilian study [9], around 16 out of 151876 patients in a single-center Singaporean study (2007–2012) [10], 1 in 18600 in a Japanese study [11], 2.6 in 100000 in a South Korean study, 1 in 11000 in an Australian study, 1 in 1280 in a French study, 2.1 in 10000 in a Thai study, 1 in 10263 in a Spanish study [12], and 1 in 10000 cases in NAP6 study in UK [6].

The true incidence of anaphylactic reactions with their associated morbidity and mortality remains poorly defined, as a good sum of these reactions is under-reported, or rather under-recognized [13]. In NAP6 particularly, the exclusion due to reporting delays or incomplete data makes the true incidence may be 70% higher than calculated [6]. Despite the reported variations, the proportion of IgE-mediated reactions seems to be relatively similar between countries, ranging from 50% to 60% [8].

However, substantial variability regarding the different drugs or agents involved is reported, reactions involving neuromuscular blocking agents (NMBAs) being more frequent in several countries, whereas allergic reactions involving antibiotics or chlorhexidine seem to be more frequent in the United States, UK and in Denmark, respectively [6,8].

3. Pathophysiology

Anaphylaxis is the classical example of immediate hypersensitivity reaction (type I) [14]. These reactions are produced by IgE–mediated (or in some cases non-IgE-mediated) release of pharmacologically active substances upon re-exposure to a specific antigen to which there has been previous sensitization. However, it can also occur on first exposure as there is cross-reactivity among many commercial household products and drugs [12,14–16].

On re-exposure, the antigen cross-links two IgE receptors on the same mast cell, triggering the reaction that eventually results in the release of preformed mediators such as histamine, tryptases, proteoglycans, and platelet-activating factor [14], which result in specific responses in different tissues (Table 1).

The non-immunologically mediated anaphylactic reaction, or what was known as anaphylactoid reaction, can result from activation of the complement cascade, without the need for an antigen-antibody interaction or IgE trigger [17].

4. Symptoms and signs: how similar they are under GA to awake patients?

It's essential that every physician should be able to recognize and treat an anaphylactic reaction once it occurs. The initial diagnosis of anaphylaxis is largely presumptive.

While symptoms in an awake patient can be easily recognized, they are usually masked under general anesthesia. All early symptoms usually observed in the awake patient such as malaise, pruritus, dizziness, and dyspnea are absent in the anesthetized patient. Most anesthetists would assume other diagnoses, such as drug overdosage or direct histamine release (e.g. with opioids) before considering anaphylaxis. Having multiple drugs needed to be administered during general anesthesia sometimes precludes identification of the culprit. Furthermore, early cutaneous symptoms may be difficult to notice in a completely draped patient, or maybe absent, and cardiovascular and respiratory symptoms may be referred as side effect of light plane of anesthesia. It's important not to limit the thought process to IV drugs, as anaphylaxis can still occur with spinal anesthesia, or even due to disinfection or intraoperative dyes.

Anaphylaxis diagnosis under general anesthesia should be suspected when all or any of the clinical features listed in Table 1 occur after introduction of a possible allergen, and the timing should be always kept in mind. It's important to keep in mind always that any of these clinical features may occur in isolation [18], in particular isolated hypotension [6], and in some severe cases the initial symptom would be bradycardia [19] or sudden cardiac arrest [8]. The absence of skin symptoms doesn't exclude anaphylaxis [8,18], as well as its presence doesn't necessitate a progression to anaphylactic shock. In a case report, authors described two case in which respiratory and cardiovascular symptoms preceded skin manifestations, which appeared 15 min after observing hypotension and decreased air entry [20]. Further studies are required to clarify the role of a fall in end-tidal carbon dioxide concentration in the early recognition and management of severe perioperative anaphylactic reactions [6].

The symptoms and signs are described according to the Ring and Messmer [21] four-step grading scale (Table 2), although other scales are also available [22]. Grades I and II are usually not life-threatening conditions, whereas grades III and IV correspond to emergency situations necessitating prompt resuscitation. It's interesting to know that immunological reactions tend to be of a higher grade and more severe than non-immunologically mediated reactions.

An old argument, which also has a valid point of view, that

Table 1
Clinical manifestation of an anaphylactic reactions.

Cardiovascular symptoms:
• Tachycardia
• Bradycardia
• Cardiac arrhythmias
• Hypotension
• Cardiovascular collapse
• Cardiac arrest
Respiratory symptoms:
• Bronchospasm
• Difficult ventilation and increased airway pressures
• Decreased $etCO_2$
Cutaneous–mucous signs
• Erythema
• Urticaria
• Angioedema

bronchospasm associated with anaphylaxis is enhanced in patients with previous asthma or COPD, especially that atopy is an established risk factor. However, a French study questioned the correlation between history of asthma and the incidence of bronchospasm during anaphylactic reaction and whether their mechanisms are related. It concluded that "history of asthma may not be related to the development of bronchospasm or the severity of intra-operative anaphylaxis. We can speculate that asthma and anaphylaxis are due to different mechanisms of increased airway resistance. This also suggest that bronchospasm occurring during anesthesia should be consider to be due to anaphylaxis rather than to asthma" [23]. In patients with asthma, the occurrence of bronchospasm or high airway pressures should not automatically be attributed to acute asthma, as, in these patients this may be the presenting feature of life-threatening anaphylaxis [6].

Diagnosing anaphylaxis under spinal anesthesia might be confusing. The patient might report early symptoms, but these symptoms of collapse and difficulty breathing might resemble those of high or total spinal. Also, local anesthetic systemic toxicity (LAST) is always a possibility that should be ruled out. Also, the collapse in circulation and blood pressure will be more pronounced given the effect of sympathectomy that occurs with spinal anesthesia. In a case report published recently, a patient developed seizure and cardiovascular collapse during a knee replacement procedure under spinal anesthesia [24]. This is a typical presentation for LAST and might easily divert the attention of the team from a possibility of anaphylaxis. After resuscitation and stabilization of the patient, the team picked a cephalosporin antibiotic as the cause of this collapse. They recommend that "timing of antibiotic administration should be adjusted for spinal anesthesia cases to allow time to detect possible anaphylaxis" [24].

Kounis syndrome is acute coronary syndrome associated with anaphylaxis [25]. It may also be referred to as allergic angina or allergic myocardial insufficiency. Following an allergic stimulus, the activation of mast cells leads to histamine, leukotrienes and serotonin release, which may lead to coronary vasospasm and circulatory collapse [26]. Kounis syndrome is not limited to a specific age group [27,28]. It's important to consider such a diagnosis in the context of treating an anaphylactic reaction, as it might change the management plan a lot. For example, epinephrine can potentially, in this case, cause more ventricular dysfunction in an already ischemic heart rather than the desired supportive effect. It's still a debated issue [2,29], but nevertheless it presents a big challenge to the treating team.

Another interesting, yet frustrating, entity is anaphylaxis-induced hyperfibrinolysis. This is where activation of the fibrinolytic system occurs as a consequence of mast cell degranulation, as suggested by some experts [30–32]. Understanding this potential problem is critical, as excessive hemorrhage may aggravate the compromised circulation. Most reports describe resolution of this state spontaneously within 20–120 min, which support opting for conservative management [33].

It's important not to jump directly to a diagnosis of anaphylaxis with each and every hypotension and/or bronchospasm. A high level of suspicion should be always present, but a list of differentials should also be in mind (Table 3). In many mild cases with a single symptom, it's very common to observe a spontaneous recovery, even with no intervention [22], which again adds to the problem of misdiagnosis or underdiagnosis. This is a big concern, as these undiagnosed incidents with no proper allergy testing will lead to a future fatal re-exposure.

Some anaphylactic reactions, although rare, occur in a "biphasic pattern"; the symptoms recur after initial resolution within 72 h, with or without treatment without re-exposure to the trigger. This was found to account for 0.4% of all anaphylaxis incidents diagnosed in emergency department in one study, and therefore the old argument to keep the patient under closed observation for at least 8 h is no longer a very solid argument [34].

5. The usual suspects

Several drugs and agents are known to cause perioperative allergic reactions. Not only drugs directly related to anesthesia, but also agents that are used by other team members, like disinfectants and dyes. Among all, muscle relaxants and antibiotics are the most frequently cited as causative agents.

5.1. Muscle relaxants

Neuromuscular blocking agents (muscle relaxants, NMBA) are accused for 60–70% of all perioperative anaphylactic reactions [35,36]. However, recent studies from UK; NAP6, reports that antibiotics are becoming the most common cause followed by NMBAs [6].

Succinylcholine (suxamethonium) is known to have the greatest risk among them all, although it's structurally homologous to acetylcholine [37]. Pancuronium and cisatracurium are the NMBAs associated with the lowest incidence of anaphylaxis during anesthesia. However, rocuronium is becoming more common cause of anaphylaxis, accounting for most of cases reported in NAP6, which may be attributed to more frequent use [6,11].

Significant differences are observed concerning the frequency of IgE-mediated reactions between countries [12]. High incidence is reported in France, Australia and New Zealand, UK, Norway, Belgium and Spain, where low incidence is reported in Sweden,

Table 2
Ring and Messmer grade of severity for quantification of immediate hypersensitivity reactions.

Generalized cutaneous signs: erythema, urticaria, with or without angioedema	I
Moderate multiorgan involvement with cutaneous signs, hypotension, and tachycardia, bronchial hyperreactivity: cough, difficulty to inflate	II
Severe life-threatening s multiorgan involvement: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm. Cutaneous signs may be present or occur only after the arterial blood pressure recovers	III
Cardiac and/or respiratory arrest	IV

Table 3
Differential Diagnosis of anaphylaxis.

Common diagnostic dilemmas:
1. Acute asthma
2. Syncope
3. Anxiety/panic attack
4. Acute generalized urticaria
5. Aspiration of a foreign body
6. Cardiovascular (myocardial infarctiona, pulmonary embolus)
7. Neurologic events (seizure, cerebrovascular event)
Postprandial syndromes:
1. Pollen-food allergy syndrome
2. Monosodium glutamate
3. Sulfites
4. Food poisoning
Excess endogenous histamine:
1. Mastocytosis/clonal mast cell disorders
2. Basophilic leukemia
Flush syndromes:
1. Peri-menopause
2. Carcinoid syndrome
3. Autonomic epilepsy
4. Medullary carcinoma of the thyroid
Nonorganic Disease:
1. Vocal cord dysfunction
2. Hyperventilation
3. Psychosomatic episode
Shock:
1. Hypovolemic
2. Cardiogenic
3. Distributived
4. Septic
Other:
1. Nonallergic angioedema
a. Hereditary angioedema types I, II, & III
b. ACE inhibitor-associated angioedema
2. Systemic capillary leak syndrome
3. Red man syndrome (vancomycin)
4. Pheochromocytoma (paradoxical response)

Denmark and USA [12].

Neuromuscular blocking agents induce an IgE-dependent reaction with the quaternary ammonium (NH_4^+) structures as main antigenic epitope [12]. Non-allergic anaphylaxis may occur with atracurium and mivacurium. Recent evidence implicates specific receptors on the surface of mast cells. Variation in receptor expression may explain why these drugs cause dramatic non-IgE-mediated mediator release in some individuals [38].

Cross-reactivity between NMBA, estimated to be about 65% by skin testing and 80% by radioimmuno-assay (RIA) inhibition tests, is believed to be due to common ammonium groups in their structure [3,12]. It is, however, unusual that an individual is allergic to all NMBA. Because of this frequent but not systematic cross-reactivity, all available NMBAs should be tested [39].

Many over-the-counter drugs, cosmetics, and food products contain quaternary or tertiary ammonium ions that could sensitize general population, and this will result in reaction upon first exposure to a muscle relaxant [11]. Neostigmine and morphine also contain ammonium ions, that may show cross-reactivity with NMBA [40].

It was demonstrated that the availability of pholcodine-containing cough syrups was responsible for sensitization of Norwegians against morphine and other ammonium-containing products [16,40]. This hypothesis was later confirmed when withdrawal of pholcodine containing syrups from the Norwegian market resulted in decrease in IgE against morphine and decrease in overall rate of NMBA-related anaphylaxis [15].

It's worth mentioning here the growing reports about anaphylactic reactions from sugammadex; a γ-cyclodextrin designed to encapsulate steroid NMBA (e.g. rocuronium, vecuronium) [41–43]. The Japanese Society of Anesthesiologists has issued a warning about sugammadex-induced anaphylactic shock five times since March 2011. The third one, issued in June 2013, included 95 cases of sugammadex related allergies that occurred between April 2010 and January 2013, although no incidents of death [11].

One systematic review of sugammadex related anaphylaxis [42] concluded, however, that the safety profile of sugammadex is good, but “awareness must be raised about the possibility of drug-induced hypersensitivity during the critical 5-min period immediately following administration, which, with prompt treatment, should be easier to manage and have a better prognosis than with delayed treatment”. NAP6 report states that there remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium induced anaphylaxis specifically and clinical trials would provide valuable evidence [6].

5.2. Antibiotics

Penicillin is the most common cause of anaphylaxis in the general population. Coming to anesthesia, the antibiotics most commonly involved in anaphylactic reactions are β-lactams, cephalosporins, teicoplanin, quinolones, metronidazole and vancomycin [6]. Antibiotics are considered the second leading cause of anaphylactic reactions in the surgical patient [12], although NAP6 reports them as number one cause [6]. There is a strong argument for antibiotics to be administered several minutes before induction of anesthesia. There are several potential benefits: first, lack of allergy can be confirmed with the patient immediately before administration, second, the severity of physiological derangement due to anaphylaxis may be lessened, and third, investigation of anaphylaxis is considerably simplified if fewer drugs have been administered [6].

A recent meta-analysis suggested that patients allergic to penicillin or amoxicillin have a higher incidence of allergic reactions to first generation cephalosporins and cefamandole but not to later-generation cephalosporins [44]. A recent systematic review showed that presence of allergy to penicillin increases the risk for anaphylactic reaction to muscle relaxants [45]. Another study found that allergy to penicillin increases the risk threefold for an individual to be allergic to any other drug [45].

Vancomycin causes a reaction known as “red man syndrome”, that consists of pruritis, erythema of head and upper trunk and hypotension [46]. It's more related to the rate of infusion rather than an immunological mechanism, and can be prevented easily by decreasing the rate of administration (over 2 h), proper dilution of the drug (200 mL), and premedication with antihistamines before the first exposure [46]. Teicoplanin can also cause red man syndrome [46].

Antibiotics like bacitracin or rifamycin, which are usually used in wound irrigation, might cause potentially life-threatening reactions, and they are usually overlooked.

5.3. Latex

Latex is a fundamental component in a wide range of perioperative products; surgical gloves, tourniquets, face masks and Ambu bags, LMAs, Foley's catheters, and much more. Latex allergy is an important cause of anaphylaxis during anesthesia. Many studies rank it as the second most common cause of anaphylaxis during anesthesia in the general population [47], but more recent studies rank them even lower in line [6], as the concept of “latex-free” environment is growing.

Sensitization occurs mostly in healthcare workers, patients with spina bifida, patients who need chronic bladder care with repeated

insertion of latex catheters or chronic indwelling catheters, and in patients undergoing multiple surgical procedures, due to repeated exposure [3]. Latex sensitization (asymptomatic latex allergy) was present in 12.5% of anesthesiologists [48].

Although usually overlooked, latex could be introduced to the patient during injection through a rubber injection port in the IV set, or from the rubber stopper of a multidose vials, and in a sensitized patient this might be all what it takes to evoke anaphylaxis. Avoidance is the only effective treatment at the present time. The introduction of "latex-free environment" concept decreased the incidence and prevalence of latex allergy greatly [49]. A "latex free" emergency cart should be available to treat anaphylactic reactions. Skin test is the gold standard to diagnose latex allergy.

5.4. Non-steroidal anti-inflammatory drugs

True anaphylaxis from a NSAID can occur, and is a drug-specific condition, where a patient allergic to one drug can easily be managed with another "structurally unrelated" drug [50]. Selective COX-2 inhibitors rarely cause anaphylactic reactions and are generally (but not always) well tolerated [51].

Hypersensitivity to paracetamol seems to be rare and evidence for an IgE-mediated mechanism is anecdotal. One Australian case report describes two patients who received paracetamol intravenously for pain control perioperatively and developed severe allergic reaction, although they lack history of allergy to paracetamol. Both patients had history of asthma and eczema and allergy to some drugs, but not paracetamol, and they both were exposed to paracetamol orally in the past with no reactions. Further skin tests confirmed that the cause of this reaction was one of the excipients (mannitol) [52].

5.5. Colloids

Anaphylaxis to colloids may be difficult to diagnose since they are usually administered in hypotensive patients. The incidence has been estimated to range from 0.033% to 0.22% [12]. These reactions usually start 20 min after starting infusion. Anaphylaxis is more frequent with gelatins (0.34%) than with dextran (0.27%), albumin (0.1%) or hydroxyethylstarch (0.06%) [12,53]. Colloids, however, are losing popularity owing to their side effects [54].

Patients at risk might include those with prior documented drug allergies and males [53]. Although some might think that allergy to eggs contraindicates administration of human albumin, this is not true. Ovalbumin, the principal protein in eggs, is different from human serum albumin, and doesn't show cross-reactivity [55].

5.6. Hypnotics, opioids, and other induction agents

Anaphylaxis to thiopental or propofol is rarely reported, whereas anaphylaxis to etomidate and ketamine remains extremely rare [6]. Allergic reactions to benzodiazepines are extremely rare [56]. Propofol was originally formulated with the surfactant Cremophor EL as a vehicle, but hypersensitivity reactions pushed towards a change in the formulation [57].

A common belief that egg-allergic individuals are at risk of developing allergic reactions when propofol is administered. A recent Danish study published in 2016 concluded that there's no much evidence supporting this assumption, nor the assumption that soy or peanut allergies are contraindications either (propofol preparation contains soy and peanut extracts) [58].

Narcotics are a common cause of flushing and urticaria following intravenous administration. Anaphylaxis, in contrast, is very rare. Morphine is a known cause of nonimmunological histamine release, and meperidine causes nonimmunological histamine release more often than any other opioid [59]. There is cross-reactivity between different opioids of the same family, but not between phenylpiperidine derivatives [3].

5.7. Local anesthetics

One should differentiate between local anesthetics systemic toxicity and anaphylaxis; the latter being very uncommon, and mostly related to the common metabolic product of the ester local anesthetic, para-amino benzoic acid [12,60,61]. Ingredients included in local anesthetic solutions such as antioxidants or preservatives including metabisulfite or parabens (also metabolized to para-amino benzoic acid) may also elicit allergic or adverse reactions [61]. There are some encounters on allergy to a few drugs of amide derivatives, namely lidocaine and mepivacaine [61].

5.8. Chlorohexidine

Chlorhexidine is a commonly used antiseptic and disinfectant used in the perioperative period for its broad-spectrum activity to bacteria, mycobacteria, and some viruses and some fungi as well [12]. It's also a very common ingredient in a number of mouthwashes, toothpaste, dressings, ointments, and over the counter disinfectant solutions [8,12], which might sensitize general population even before exposure perioperatively [8]. Significant geographical differences are reported concerning the incidence of chlorhexidine-induced anaphylaxis. Reactions are quite frequent in UK or Denmark but relatively rare in France, under-recognition and differences in practice [6,12].

Several case reports have been published about life-threatening reactions from chlorhexidine; full-blown anaphylaxis after dialysis site paint with confirmed skin testing [62], refractory anaphylaxis after surgical paint requiring ECMO support [63], anaphylaxis after topical application for dental procedure [64], anaphylaxis during an LVAD procedure [65], and several others [66,67]. Surprisingly, although povidone-iodine (betadine) is a commonly applied topical antiseptic solution, anaphylaxis to this compound is rare [68].

Clinical teams should be aware of 'hidden chlorhexidine' such as in urethral gels and coated central venous catheters, and should consider this as a potential culprit if perioperative anaphylaxis occurs [6].

6. Management: diagnose early, act early

Management of anaphylaxis is not only managing the acute reaction in OR settings, but more importantly preventing this reaction from occurring by carefully taking history and adjusting anesthesia plan accordingly, and identifying patients with previous exposure and reactions to label them correctly to prevent re-occurance.

A careful history regarding adverse drug reactions and allergies should be conducted before any surgical procedures requiring anesthesia. Risk factors should be sought; e.g. patients with a past/family history of atopy might be at risk [69], and may affect the severity of anaphylactic reactions and patient response to treatment [70]. For example, patients with asthma and cardiovascular disease are more likely to experience a poor outcome from anaphylaxis [70]. Those patients shouldn't be given suspected drugs if possible, and their management plan should contain alternatives. It's also important to label the patients carefully, and those who had previous grade I or II reactions should be investigated and warned against the use of these medications in the future. Of course, patients with a full picture of anaphylaxis will be investigated thoroughly, and documentation and patient education

play a crucial role in their future management.

H_1 and H_2 blockers or corticosteroids before surgery could minimize the severity of anaphylaxis, but may also blunt the early signs of anaphylaxis, leaving a full-blown episode as the presenting sign. These drugs should be reserved for the early treatment of anaphylaxis [67].

The clinical manifestations of intraoperative reactions differ from those of anaphylactic reactions outside of anesthesia as these patients are draped and cannot complain of cutaneous symptoms such as pruritus or a sense of flushing, especially under GA. Moreover, concomitantly administered drugs may alter the expression and degree of clinical manifestations. The difficulty in recognizing anaphylactic symptoms in anesthetized subjects may also be explained by the need to exclude various other clinical conditions.

Vigilance should be exercised all the time to avoid fatal outcomes. Prompt and early recognition and treatment can significantly change the outcome, even with a severe reaction. In a series of 164 fatalities due to anaphylaxis, the median time interval between onset of symptoms and respiratory or cardiac arrest was 5 min in iatrogenic anaphylaxis, 15 min in stinging insect venom-induced anaphylaxis, and 30 min in food-induced anaphylaxis [71].

Departments of anesthesia should have protocols for the detection, management and referral for investigation of perioperative anaphylaxis. These should be readily accessible to all departmental members, widely disseminated and kept up to date, and perioperative anaphylaxis guidelines and/or a management algorithm should be immediately available wherever anesthesia is administered [6]. Where a critical perioperative hypotensive event occurs, and perioperative anaphylaxis is one of several differential diagnoses, treatment for anaphylaxis should start promptly as there is little to be lost and much to be gained [6]. An outline of acute management could be found in Fig. 1.

Additional precautions and considerations are important in the management of anaphylaxis in pregnant women (left lateral tilt, continuous fetal monitoring, etc.) [71]. Anesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients [6]. Epinephrine should not be withheld for fear of a detrimental effect on placental perfusion [6].

6.1. Stop the causative agent

After recognition of the event, the first step is to stop the administration of all agents likely to have caused the anaphylaxis and call for help. Maintaining airway is important, and 100% oxygen should be administered to increase oxygen delivery and compensate for the increased oxygen consumption, and the patient should be positioned in Trendelenburg position [71].

6.2. Epinephrine

Epinephrine is the first line drug in management of acute anaphylaxis, and can't be substituted by any other medication, such as antihistamines or steroids [72]. Through the activation of α- and β-adrenergic receptors, epinephrine functionally antagonizes all of the important pathophysiology of anaphylaxis by vasoconstriction, reduction of vascular permeability, bronchodilatation, edema reduction and positive inotropy in the heart [6]. Administered intravenously, it shows the fastest onset of action of all anaphylaxis drugs [73]. Subcutaneous injection of epinephrine is no longer recommended because of insufficient absorption resulting in delayed onset of action [73].

Epinephrine can and should be repeated after 5 minutes until there's an adequate sustained response [74]; the administration of other medication such as antihistamines or steroids must not cause delay or distraction, as these are not first-line (or even second-line) treatments for anaphylaxis [75]. Delays in treating with epinephrine are a risk factor for fatal outcome [75]. In case of an unstable patient, a continuous infusion of approx. 0.05–1 μg/kg/minute is effective [73].

IV epinephrine infusions should be used with a dedicated line, infusion pump and anti-reflux valves wherever possible. If no infusion pump is available the recommendation is to mix 1 mL of 1:1000 epinephrine in 1000 mL of normal saline and start infusion at 5 mL/kg/hour (~0.1 μg/kg/minute), titrating rate up or down according to response with close monitoring [76]. IV boluses of epinephrine are not recommended without specialized training as they may increase the risk of cardiac arrhythmia [76]. Epinephrine is recommended in pregnancy [73]. In case of severe life-threatening anaphylaxis there is no absolute contraindication for epinephrine, not even coronary artery disease [6,73]. Epinephrine doses for children are listed in Fig. 1. Epinephrine should be diluted properly to avoid serious cardiovascular side effects.

6.3. Antihistamines

Some physicians believe that antihistamines can treat anaphylaxis and epinephrine is only needed when everything goes wrong, which is definitely not true [75]. Oral antihistamines take around 30 min for onset of effect; intravenous chlorphenamine has a faster onset but can cause hypotension. Antihistamines are not effective against anaphylaxis [75]. NAP6 found no evidence of either benefit or harm of antihistamines, and further research is needed to prove or disprove their role in resuscitation [6]. It may reduce angioedema and urticaria.

6.4. Steroids

Historically, corticosteroids have been used to prevent protracted and biphasic reactions. However, this has never been tested in a randomized clinical trial; more recent evidence has cast doubt over their efficacy [75]. Around 50% of the second phase of biphasic reactions occurred >11 h after initial reaction. This led to the current guidance from the National Institute for Health and Care Excellence (NICE) who recommends patients over 16 years should be observed for 6–12 h after anaphylaxis (children under 16 should be admitted) [75]. In reality, it is generally accepted that prolonged observation may not be required following a straightforward reaction in someone who already has a comprehensive management plan and rescue medication (including epinephrine autoinjectors) in place [75].

6.5. Other vasoactive agents

Dopamine, norepinephrine and vasopressin can also be applied in life-threatening situations [73]. If epinephrine and volume substitution are insufficient to control symptoms, dopamine can be administered as a continuous intravenous infusion instead of epinephrine. The usual dose is 2–15 μg/kg/minute [73].

Norepinephrine is used when the effect of volume substitution and epinephrine/dopamine is insufficient. Due to its marked vasoconstrictive effect, it should be administered only as a continuous intravenous infusion under strict blood pressure and pulse monitoring. The usual dose is 0.02–0.15 μg/kg/minute [73].

Glucagon (especially if the patient is receiving β-blockers) can be administered if these drugs failed to restore circulation (after adequate volume resuscitation) [72], and according to the NAP6 recommendations it should be available within 10 min if a reaction is identified, so it will be immediately available if needed [6]. The recommended dose of glucagon is 1–5 mg (20–30 mcg/kg

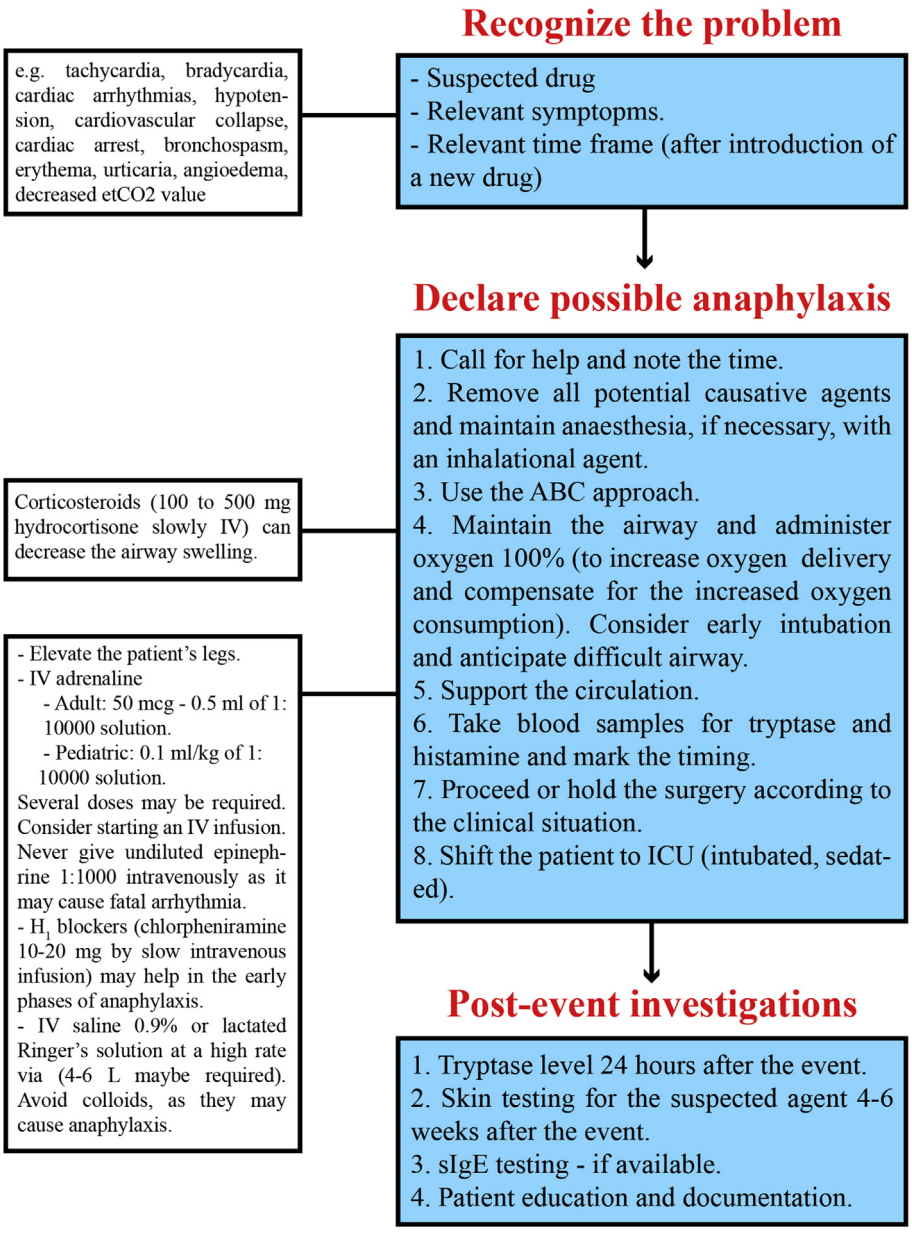

Fig. 1. Management algorithm of acute phase of anaphylaxis.

[maximum, 1 mg] in children) administered intravenously over 5 min and followed by an infusion of 5–15 mg/min titrated to clinical response [72].

Administration of IV vasopressin 2 units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory [6].

6.6. Fluid management

An important pathophysiological aspect of anaphylaxis is the resulting hypovolemia which is treated with adequate volume substitution. For severe anaphylactic reactions, the supply of large amounts of fluid within a short time is necessary through large-bore venous access (ideally 16 or 14 gauge in adults) [71]. Around 0.5–1 L, and possibly up to 2–3 L of fluid – depending on the response – in a very short time is required for adults, for children initially 20 mL/kg body weight [6,73].

Normal saline (NaCl 0.9%) or balanced electrolyte solutions should be used. When large quantities of electrolyte solutions are given, they remain in the intravascular space for a short time only. Therefore, failing stabilization after the application of larger volumes of electrolytes (>1 L) the additional application of colloid volume substitutes can be considered, but with extreme caution, as they themselves can lead to anaphylaxis [73]. Some recommend against use of colloids in fluid resuscitation, and even to replace the IV set of the patient (during resuscitation) if it was used to give colloids at the time of the event [6].

6.7. Other modalities for circulation support

There are some recommendations to consider ECMO in patients in whom resuscitation with conventional methods fails [72], backed by some case reports [63]. The decision to initiate ECMO can be difficult but should be considered early in patients who are failing to respond to traditional resuscitative measures and before irreversible ischemic acidosis develops [72].

It's also recommended by NAP6 to start CPR immediately if during an anaphylaxis systolic blood pressure dropped to <50 mmHg in adults, even without cardiac arrest. It should be simultaneously with immediate treatment with epinephrine and liberal IV fluid administration [6].

6.8. Airway management

The threshold to intubate should be very low, and intubating a patient who is awake, or converting from an LMA to an ETT could be lifesaving if done on time. One shouldn't wait till there's significant edema and airway obstruction that hampers patient's breathing and significantly complicate the management and increase morbidity and mortality. In a minority of cases, an emergency cricothyroidotomy may be required to secure the airway if upper airway edema prevents access to the glottic aperture [71].

6.9. Post-incident investigations

An important part of managing these cases is to confirm the nature of the reaction. It is important to conduct three basic diagnostic tests: biochemical determination (e.g. tryptase and histamine), serological determination (sIgE) and skin tests.

Tryptase is a mast cell neutral serine protease that can be of great value for diagnosis of mast cell disorders. Serum tryptase level reaches a peak 15 min to 1 h after release, and declines with a half-life of 2 h. It's, therefore, important to correctly and timely collect the sample for tryptase level, maximally between 15 and 60 min for grade I and II, and between 30 min and 2 h in grade III and IV. An increase of total tryptase concentrations is highly suggestive of mast cell activation as seen in anaphylaxis. Another sample should be taken at least 24 h after the event or later when the patient is investigated to compare the initial samples to the baseline [77]. Blood samples taken before this time window might show high levels and will not reflect the baseline [13]. The absence of increased serum tryptase doesn't exclude allergic reactions [7].

Skin tests coupled with positive history remain the gold standard for the detection and confirmation of anaphylaxis by exposing the mast cells of the skin to the suspected allergen [78]. A 4- to 6-week delay after the reaction is required to avoid a false-negative test result because of mast cells stores depletion [78,79]. All skin testing should be at concentrations validated to be below the non-specific histamine-releasing/irritant concentrations (as published and verified locally) [6].

None of the available diagnostic tests demonstrates absolute accuracy [80]. False-positive test results may cause inconvenience (unnecessary avoidance of a safe drug), whereas false-negative or equivocal results may be extremely dangerous and severely undermine correct secondary prevention.

Avoidance advice should be specific and not excessive, as this may lead to harmful consequences. When no culprit agent is identified, further investigations should be carried out rather than giving 'blanket advice' on avoidance of multiple drugs [6]. Ideally, diagnosis of anaphylaxis during anesthesia should rest upon different confirmatory tests, rather than on a single one. It must be kept in mind that some patients might suffer from multiple allergies [6].

7. Developing a protocol

Incorporating anaphylaxis in core training of all anesthetists and developing local protocols and pathways is fundamental. A known algorithm, that's based on recent updated guidelines, can save lives by minimizing the human error and mental block that might accompany such acute unexpected events [6].

Availability of anesthesia anaphylaxis treatment packs, including an anaphylaxis management algorithm, adrenaline prefilled syringes suitable for IV administration, hydrocortisone and details of the location of glucagon and vasopressin is highly recommended [6]. This should be immediately available wherever anesthesia is administered. Anesthesia anaphylaxis investigation packs, including tryptase sampling tubes and paperwork that describes details of blood tests required and their timing, instructions on referral for further investigation and allergy clinic details and documentation for the patient, should also be available in all theatre suites [6].

8. Is it wise to continue the surgery?

The question might look simple, but the decision to abort the procedure or continue it may be challenging. If the procedure didn't start yet in an elective setting, it's easy to decide to abort it until the patient is stabilized, and reschedule the patient after full investigations and workup. However, in some scenarios this might not be feasible. Abandoning the planned surgery may harm the patient by allowing progression of his disease, cause inefficiencies in the healthcare system and social inconvenience [81].

None of the established guidelines written by several concerned bodies (e.g. Association of Anaesthetists of Great Britain and Ireland, the Scandinavian Society of Anaesthesiology and Intensive Care Medicine Clinical Practice Committee, the Joint Task Force of Practice Parameters) addressed this question despite its importance. Despite mentioned in the 2013 Australia and New Zealand Anesthetic Allergy Group (ANZAAG) recommendations that abandoning vs. continuing should be considered, there is no specific criteria or clear instructions about this point [81], although NAP6 report clearly recommends that non-essential surgery should not be started after severe perioperative anaphylaxis, and if the reaction occurred during a non-essential surgery the operation should be curtailed unless there is an overriding reason to continue [6].

An observational study by Sadleir et al. in Western Australia examining patients with anaphylactic reactions who either completed the procedure or didn't over a period of 10 years (2005–2014) and looked into the outcome. The results showed that patient with grade 1 or 2 didn't suffer any major events despite proceeding with surgery. In patients with grade 3 or 4 the decision to abandon the scheduled surgery didn't show to significantly alter the rate of complications or decrease the risk for adverse events [81].

The classical teaching to abandon the surgery in case of adverse allergic event doesn't seem to be strongly validated [81]. Nevertheless, it may be justified to continue the surgery if the initial resuscitation methods were successful, or the surgery will not interfere with the resuscitation [81]. This might be limited to one population and further observations must be made on other groups before generalizing these recommendations.

It's always helpful to discuss such a decision in a multidisciplinary approach, actively involving the surgical team in the process, and stating clearly both risks associated with proceeding and risks associated with aborting the procedure. Patient safety comes first, but in some instances the safety of the patient might be compromised if the procedure was held at a critical step. We believe that such a decision is highly individualized and is the responsibility of both the anesthetist and the surgeon.

9. Conclusion

Anaphylaxis remains, despite all this growing knowledge, a shadowy realm. We can't for sure predict who might develop a reaction and which medicine might illicit it. Although we have lots

of diagnostic tools available that greatly improved the overall recognition and decreased the future incidents, reliability remains an issue, and lacking tests for common allergens is still an obstacle to be overcome. It should always be a differential diagnosis of any collapsing patient perioperatively.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tacc.2019.04.005.

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