Anaphylaxis
Clinical presentation and perioperative management

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Definition: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death"

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The European Academy of Allergology and Clinical Immunology committee recommended that the term *anaphylactoid*, introduced for non–IgE-mediated anaphylactic reactions, should no longer be used (not universally accepted yet).

Introduction

Anaphylaxis during anaesthesia is a rare phenomenon, but may have life threatening consequences when encountered and if not managed appropriately. The anaesthetist is usually alerted to a crisis only when it is severe enough to cause rapid cardiovascular and respiratory compromise.

Early signs and mild symptoms remain virtually unrecognised when patients are unconscious and covered with surgical drapes, preventing observation of the initial skin manifestations. Secondly, the severity of the reaction may be underestimated by the anaesthetist. The cardiovascular deterioration may initially be masked by a light plane of general anaesthesia (or an extensive regional block). Conversely, hypotension and difficulty in ventilation may have other more common causes that need to be excluded first.

Multiple drugs are administered over a short period of time and allergenic agents are not limited to intravenous drugs or fluids. It may include other substances used in the operating room such as skin disinfectants, latex gloves and catheters. Skin or mucosal application leads to a delayed onset of reaction, often presenting 15-30 minutes into a procedure.

Pathophysiology

Anaphylaxis is an immediate immunologically mediated allergic reaction to an administered substance. It is classified as a type 1 hypersensitivity reaction involving multiple organ systems. It can be IgE- or non IgE-mediated.

The clinical manifestations are due to the immediate as well as on-going release of preformed mediators from mast cells and basophils. Initial sensitisation occurs when T lymphocytes in susceptible patients are presented with an allergen and in response produce **IgE antibodies**. The IgE antibodies bind to high affinity FcεRI receptors on mast cells and basophils (as well as low affinity FcεRII of leucocytes, platelets and eosinophils). This initial phase of sensitisation is clinically silent.

Re-exposure to the allergen cause multimeric cross-linking of the IgE antibodies, activating intracellular transduction cascades with the release of preformed mediators (histamine, tryptase, chymase and heparin) from mast cells and basophils. This triggers the release of pro-inflammatory phospholipid derived mediators (prostaglandin D2, leukotrienes, platelet activating factor (PAF), thromboxane A2). These mediators in turn cause the release of chemokines and cytokines, with the recruitment of inflammatory cells. A very small amount of antigen is needed to activate this severe allergic cycle.

The involved target organs are usually skin, mucous membranes, cardiovascular and respiratory systems, as well as the gastrointestinal tract. The corresponding clinical signs are described by the Ring and Messmer clinical severity scale (Grades I – IV).

Grade	Symptoms			
	Skin	*GI*	*Respiratory*	*Cardiovascular*
I	Local pruritis Flushing Urticaria Angioedema			
II	Same as above	Nausea Cramping	Rhinorrhea Hoarseness	Tachycardia (>20 bpm) Blood pressure Δ (>20 mmHg systolic) Arrhythmia
III	Same as above	Vomiting Defecation Diarrhea	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Same as above	Same as above	Respiratory arrest	Cardiac arrest

Non IgE-mediated immunologic type 1 reactions are clinically indistinguishable from IgE-mediated reactions. It can however occur on first exposure to the allergen. **IgG-mediated** reactions are much less frequent and less serious than IgE-mediated reactions. Histamine release may also be idiopathic or triggered directly (physical factors like cold or heat, drugs like morphine, atracurium, meperidine and vancomycin), or may be released in response to bradykinin or complement activation. The clinical response depends on both the drug dose and the rate of delivery, but is usually benign and confined to the skin.

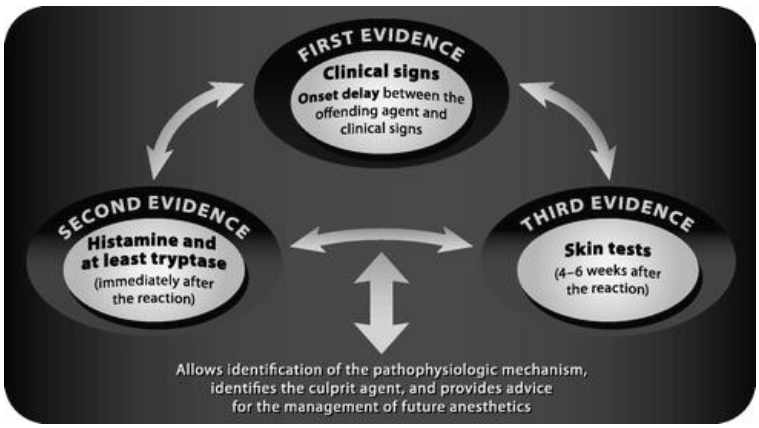
Epidemiology

The overall incidence of perioperative anaphylaxis is estimated at 1 in 10 000 – 20 000 anaesthetic procedures. It is estimated at 1 in 6500 administrations of neuromuscular blocking agents. Females are more affected than males. The exact incidence remains underestimated as reactions are underreported. Morbidity rates due to perioperative anaphylaxis remain unknown, but between 3 -10% of mortality rates (France, United Kingdom) that are partially or totally anaesthesia related involves anaphylaxis.

Allergic reactions to every drug used in anaesthesia (except the volatiles) have been documented, with neuromuscular blocking agents (NMBAs) followed by antibiotics and latex as leading causes. Anaphylaxis to NMBAs is not uncommon in patients without a known previous exposure. Quaternary ammonium ions are suggested to be the allergenic determinants in NMBAs. Commonly used household chemicals, such as toothpastes, detergents, shampoos, and cough medicines, share these same determinants with NMBAs, thereby being a contributing factor in these cases.

Clinical presentation

The etiologic diagnosis of an immediate reaction occurring during anaesthesia relies on a triad including **clinical**, **biological**, and **allergologic** evidence.



1. **Clinical:**

The initial diagnosis of anaphylaxis is presumptive as it may progress within minutes to become life-threatening. Therefore the first line of evidence for the diagnosis includes the features and severity of clinical signs as well as the timing between the introduction of the allergen and onset of symptoms. The required dosage of resuscitation drugs used also indicates the severity of the reaction.

The clinical features during anaesthesia may include:

Cardiovascular:	Tachycardia, bradycardia, cardiac arrhythmias, hypotension, cardiovascular collapse, cardiac arrest
Respiratory:	Bronchospasm
Cutaneous-mucous:	Erythema, urticaria, angioedema

(See Ring and Messmer severity scale: Grades I/II are usually not life-threatening, whereas grades III/IV are emergency situations.)

Perioperative anaphylaxis usually occurs within minutes after induction. It is primarily linked to intravenous agents. The most common presentation during severe reactions is pulselessness, desaturation and bronchospasm with difficult ventilation. Respiratory signs are exaggerated in patients that are known with underlying respiratory disease (COPD/asthma).

There are three predictive criteria for the severity of the on-going anaphylactic reaction:

- Rapid onset of reaction post-exposure to the allergen
- Cutaneous signs may be absent in rapidly progressive anaphylaxis (vasospasm of subcutaneous vascular bed during circulatory homeostasis)
- Bezold-Jarisch reflex (cardio inhibitory reflex with paradoxical bradycardia during extreme hypovolemia)

2. **Biological:**

Biochemical tests can be done *in vivo* or *in vitro.*

Primary investigation: *In vivo*

- *Histamine*: Preformed in granules of mast cells and basophils

  Early increase in plasma concentrations, plasma half-life 15-20minutes (prolonged presence in severe reactions)

- *Tryptase*: Preformed neutral serine protease in mast cells
    - Alpha-tryptase: Secreted constitutively, increased in mastocytosis (disorder of too many mast cells in the body)
    - Pro-beta-tryptase: Secreted constitutively, represent mast cell mass
    - Mature beta-tryptase: Stored in mast cell granules, reflects mast cell activation with mediator release

  Reach peak plasma concentrations 15-60 minutes, half-life approximately 2 hours. Better to compare concentrations with baseline levels taken more than 24 hours after the reaction.

Secondary investigation*: In vitro* (not available everywhere)

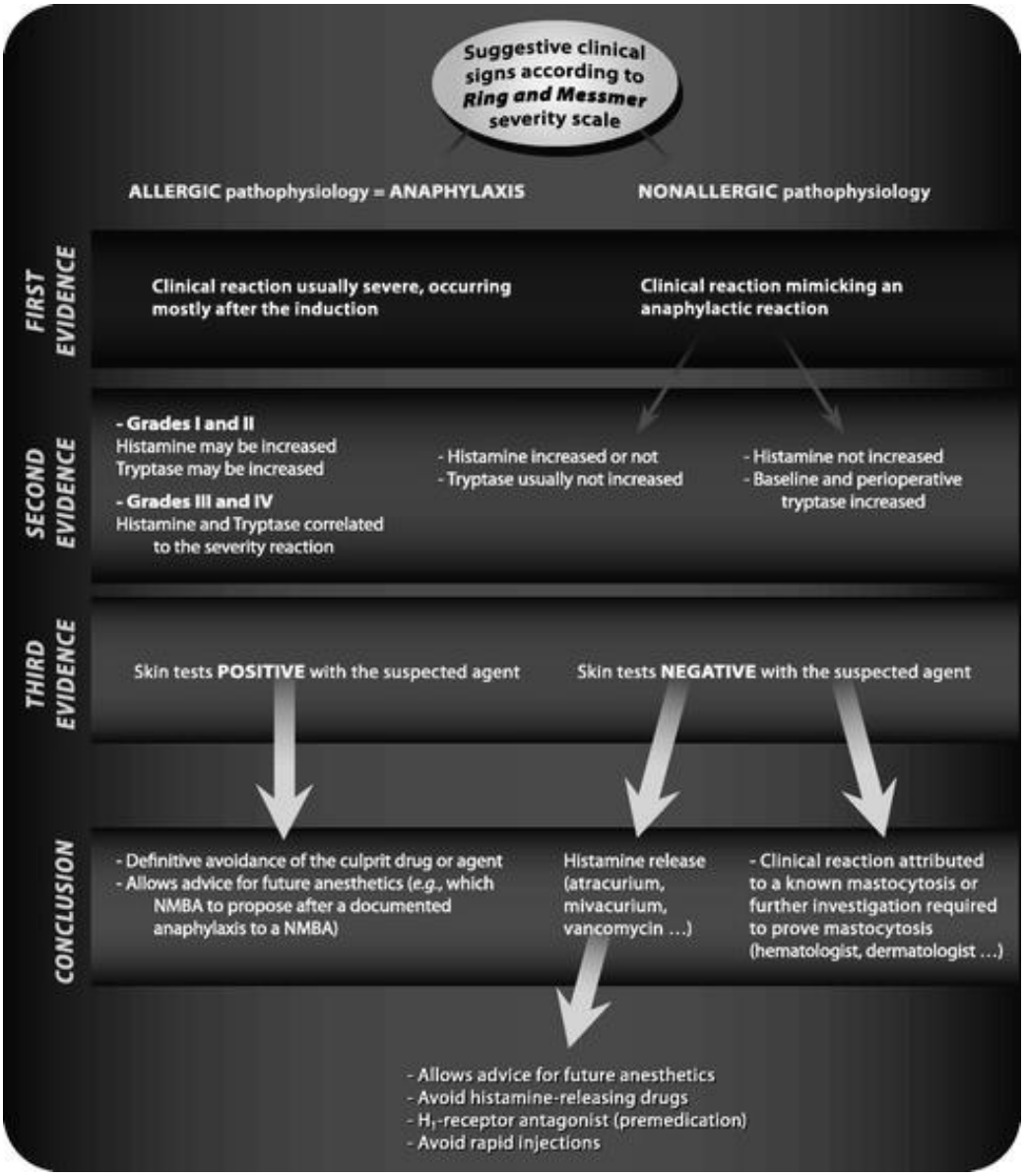
- *In vitro specific IgE assays*: Suxamethonium, Thiopental, Propofol, Amoxicillin, Cefaclor, Penicillin G/V, Latex (less sensitive than skin tests)
- *Leucocyte histamine release test*: Reliable to investigate cross-reactivity among NMBAs
- *Flow cytometric analysis*: Quantification of in vitro-activated basophils after challenge

3. Allergological/Skin Tests:

Skin tests remain the **gold standard** for IgE-mediated reactions by exposing the skin mast cells to suspected allergens. It serves to identify the culprit agent as well as the pathophysiological mechanism (allergic vs. non-allergic) to be able to suggest a safe drug alternative for future anaesthetic exposures. A 4-6 weeks delay after an anaphylactic reaction is required to avoid false-negative results.

Skin tests: Diluted or undiluted commercial solutions, Negative (saline) and positive (histamine/codeine) control

- Prick tests (PTs)
- Intradermal tests (IDTs): More sensitive/less specific, more likely to trigger systemic allergic reaction



Specific drugs

1. **Neuromuscular Blocking Agents**:

- 50-70% of perioperative anaphylaxis (suxamethonium, rocuronium)
- Previous exposure not necessary: quaternary ammonium structure in household chemicals
- Cross-reactivity between NMBAs common (60-70%)
- Benzylisoquinolones (mivacurium, atracurium) cause direct mast cell degranulation with skin changes

2. **Antibiotics**:

- Penicillins and 1st generation cephalosporins (70%) due to beta-lactam ring
- Cross-reactivity between penicillins and 1st generation cephalosporins 8-10% due to similar structure (can give 2nd/ 3rd generation cephalosporins cautiously)
- Vancomycin, if administered too quickly cause “Red Man Syndrome” due to generalised histamine release

3. **Latex**:

- Cause of 20% of perioperative anaphylactic reactions
- High risk group: Atopic patients, Food/Fruit allergies (banana, mango, kiwi...), repeated exposure to latex (repeated surgeries, spina bifida, health care workers), severe contact dermatitis
- Latex in anaesthesia: gloves, intravenous cannulas/vials, urine catheters, endotracheal tubes

4. **Other**:

- *Hypnotics*: Thiopental/Propofol rare, Etomidate/Ketamine/Benzodiazipines extremely rare
- *Opioids*: Very rare (Morphine/Codeine/Meperidine induces histamine release), cross-reactivity uncommon
- *Local Anaesthetics*: Extremely rare (Metabolite of esters, para-amino-benzoic acid may provoke IgE mediated reactions), Cross-reactivity in ester group (no cross-reactivity between ester and amide groups)
- *Colloids*: Rare, but more frequently gelatins, dextrans, albumin (Hydroxyl-ethyl starches extremely rare)
- *Dyes*: Isosulfan and patent blue rare, Methylene blue extremely rare
- *Others:* Protamine, antiseptics (chlorhexidine, povidone iodine), iodinated contrast agents (free iodine fractions)

Management of perioperative anaphylactic reactions

(Prevention in patients with previous un-investigated severe immediate reactions during anaesthesia: Regional anaesthesia with latex-free environment)

Immediate actions:

Withdraw suspected culprit

1. Discontinue anaesthetic drugs if occurred during induction
2. Maintain airway with 100% oxygen
3. Early administration of Epinephrine
4. Call for help
5. Position in Trendelenburgh position
6. Abbreviate surgical procedure/Postpone surgery

Restoration of cardiovascular homeostasis:

- Intravenous epinephrine: Titrated boluses 10-20ug (Grade I/II) or 100-200ug (Grade III/IV) +- continuous infusion (1-4 ug/min). High doses (1-3mg) with cardiac arrest during cardiopulmonary resuscitation.
- Intramuscular epinephrine 1:1000 should be administered as follows:
    - >12 years 500 ug IM (0.5 mL)
    - 6-12 years 250 ug IM (0.25mL)
    - >6 months-6 years 120 ug IM (0.12 mL)
    - <6 months 50 ug IM (0.05 mL)
- Intravascular fluids: Start rapid crystalloid/colloid boluses early to compensate for large fluid shifts due to increased vascular permeability (within 10 minutes). Adult patient may require 2-4 L of crystalloid.

Bronchospasm:

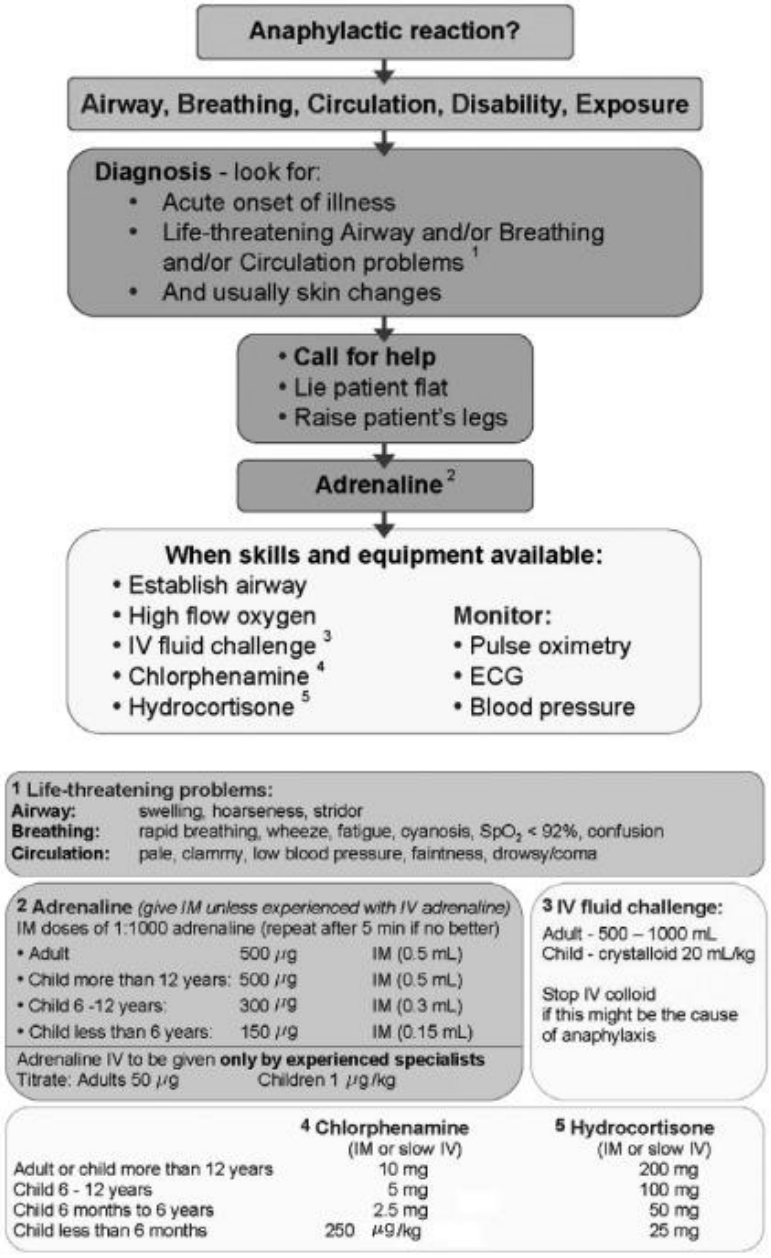
- Inhaled/Intravenous Beta2-agonists (Salbutamol/Albuterol)
- Epinephrine (Beta2-effects)
- Intravenous corticosteroids early (beneficial effects 4-6 hours later)

Additional:

- Intravenous corticosteroids and H1-receptor antagonists effects never evaluated in placebo-controlled trials

- Anaphylactic shock refractory to cathecholamines:
    - Patients on beta-blocker therapy: norepinephrine, metaraminol, glucagon
    - Vasopressin
    - Methylene blue (catecholamine- and vasopressin-resistant anaphylaxis, interfere with nitric oxide-mediated vasodilation)

(Please see RCSA algorithm at: www.resuscitationcouncil.co.za)



Summary

Anaphylaxis is a life threatening condition, more so perioperatively due to the lack of cutaneous symptoms because the patient is unconscious and draped and signs are not noticed. Adverse drug reactions and side effects are usually expected and therefore managed accordingly, whereas anaphylactic reactions are unexpected and dose independent and can occur at first exposure during anaesthesia.

Most drugs that are used during the perioperative period can cause anaphylaxis, but it is fortunately a very rare event. It is important to identify the offending agent to ensure a safe alternative for future anaesthetics by referral for skin testing post-operatively. Skin testing may unfortunately confirm the identity of the offending agent in only a minority of patients. Muscle relaxants, antibiotics and latex are the most common anaesthetic related allergens

Prevention plays an important role in the management of anaphylactic risk. Documentation during anaesthesia, referral to an allergist and appropriate labelling of the patient are essential to prevent future episodes. Patient must be fully informed and be instructed to give a thorough history.

References

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