

PRACTICAL GUIDELINES FOR PERIOPERATIVE ANAPHYLAXIS

R1 ชนิตพล/ อ.กฤษฎิ์



TABLE OF CONTENTS

01 EPIDEMIOLOGY

02 PATHOPHYSIOLOGY



03 DIAGNOSIS

04 TREATMENT

Journal of Anesthesia

<https://doi.org/10.1007/s00540-021-03005-8>

GUIDELINE



Practical guidelines for the response to perioperative anaphylaxis

Tomonori Takazawa¹ · Ken Yamaura² · Tetsuya Hara³ · Tomoko Yorozu⁴ · Hiromasa Mitsuata⁵ · Hiroshi Morimatsu⁶ · The Working Group for the Preparation of Practical Guidelines for the Response to Anaphylaxis, Safety Committee of the Japanese Society of Anesthesiologists

Received: 2 August 2021 / Accepted: 21 September 2021

© Japanese Society of Anesthesiologists 2021

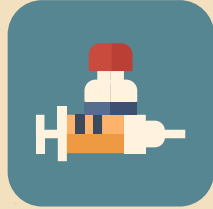
Published online: 14 October 2021



INTRODUCTION

“A hypersensitivity reaction that can cause systemic allergic symptoms in multiple organs due to invasion by allergens and can be life threatening”

IDENTIFYING THE INFORMATION



Anaphylaxis

systemic allergic
symptoms in multiple
organs



Anaphylaxis shock

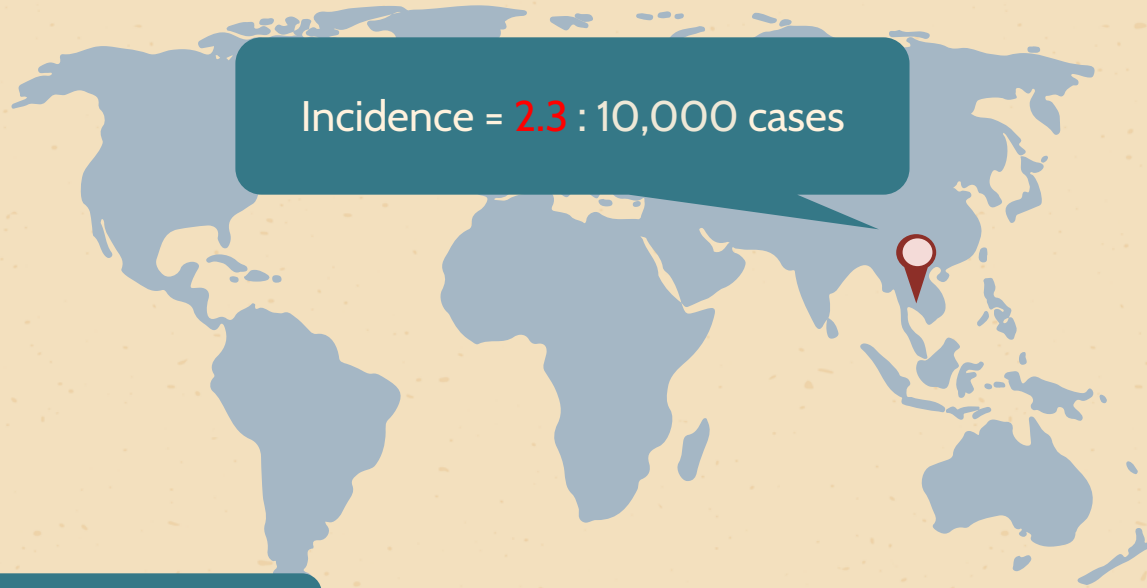
decreased blood
pressure or impaired
consciousness



01

EPIDEMIOLOGY

EPIDEMIOLOGY



Incidence = 2.3 : 10,000 cases

Incidence = 1 : 10,000 cases
Mortality rate = 4.76 %



Multicentered study of anesthesia: related mortality and adverse events by incident reports in Thailand

สมรัตน์ จารุลักษณะนันท์; Somrat Charuluxananan; ยอดยิ่ง ปัญจสวัสดิ์วงศ์; Yodying Punjasawadwong; ศิริพร ปิติมานะอารี; Siriporn Pitimana-aree; เทวรักษ์ วีระวัฒน์กานนท์; Thewarug Werawatganon; วรีณี เล็กประเสริฐ; Varinee Lekprasert; ศศิกานต์ นิมมานรัชต์; Sasikaan Nimmaanrat; อักษณ พูนิตีพร; Aksorn Pulnitiporn; วรุต ลากพิศพนธ์; Worawut Lapisatepun;

Date: 2560-09

CAUSATIVE AGENT



Muscle Relaxants

Rocuronium

Atracurium

Succinylcholine



Antimicrobial Agents

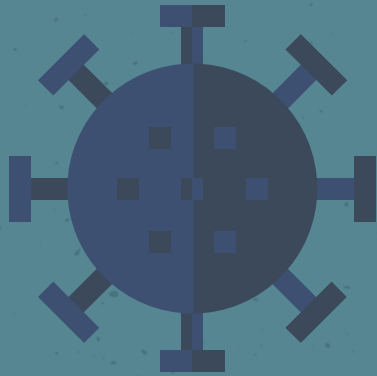
Penicillins

Cephalosporins



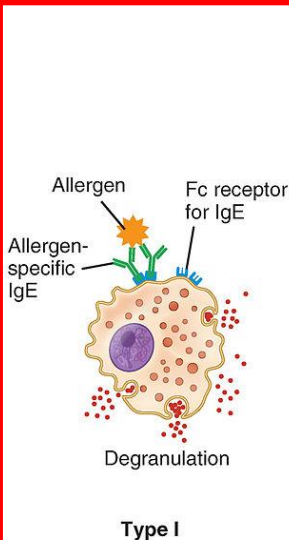
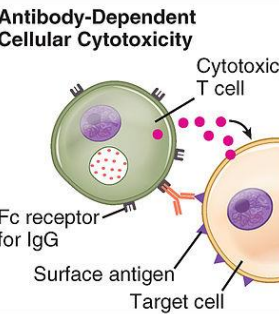
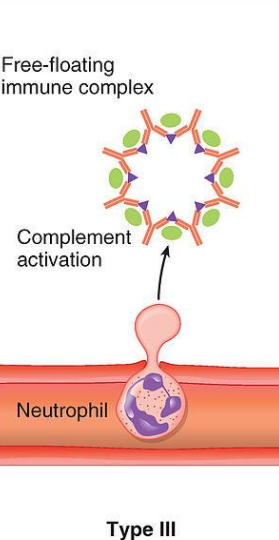
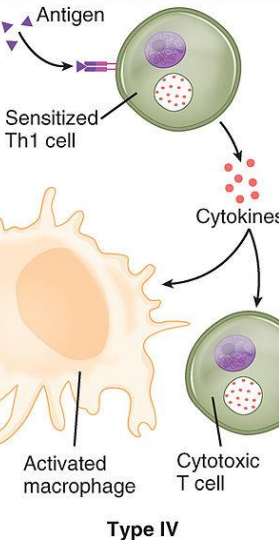
Latex





02

PATHOPHYSIOLOGY

 <p style="text-align: center;">Type I</p>	<p style="text-align: center;">Antibody-Dependent Cellular Cytotoxicity</p>  <p style="text-align: center;">Type II</p>	<p style="text-align: center;">Free-floating immune complex</p>  <p style="text-align: center;">Type III</p>	 <p style="text-align: center;">Type IV</p>
<p style="text-align: center;">IgE-Mediated Hypersensitivity</p>	<p style="text-align: center;">IgG-Mediated Cytotoxic Hypersensitivity</p>	<p style="text-align: center;">Immune Complex-Mediated Hypersensitivity</p>	<p style="text-align: center;">Cell-Mediated Hypersensitivity</p>
<p>IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.</p>	<p>Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)</p>	<p>Antigen-antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site</p>	<p>Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site</p>
<p>Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema</p>	<p>Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis</p>	<p>Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</p>	<p>Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis</p>

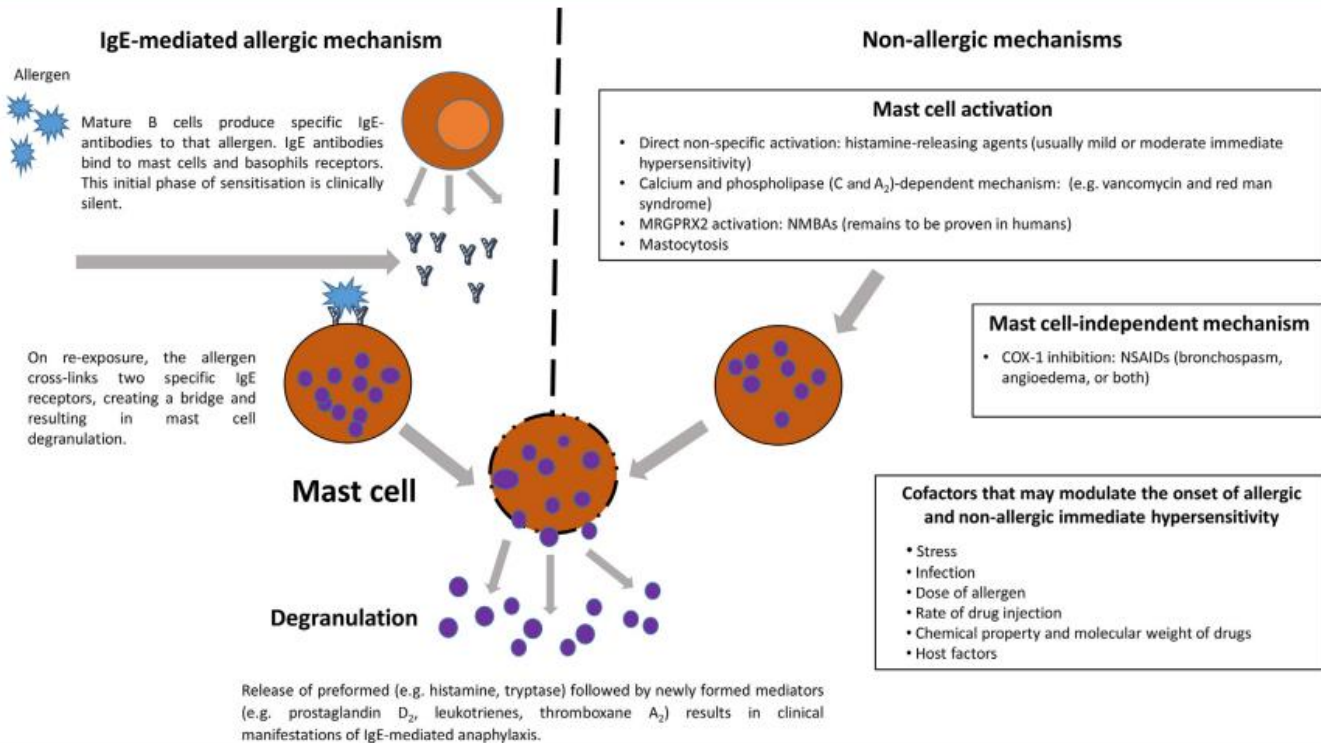
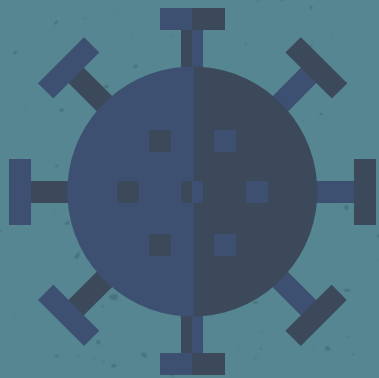


Fig 1 Pathophysiological mechanisms of perioperative immediate hypersensitivity. COX-1, cyclooxygenase 1.



03

DIAGNOSIS

DIAGNOSIS



PREOPERATIVE DIAGNOSIS

- Preoperative diagnosis
- Preoperative allergy test



PREOPERATIVE DIAGNOSIS

Preoperative diagnosis

Criteria for high risk of anaphylaxis

- Definitive diagnosis of allergies caused by drugs administered during past anesthesia
- Allergic symptoms during past anesthesia
- A previous allergic reaction to latex

PREOPERATIVE DIAGNOSIS

Preoperative allergy test

- Not need screening for allergies to anesthetics or products
- History of drug allergies, previous anesthesia records should be obtained
- Local anesthesia should be used as much as possible, or the use of muscle relaxants and histamine-releasing drugs should be avoided for patients who have had an allergic reaction during previous anesthesia

PREOPERATIVE DIAGNOSIS

Special circumstances and allergy test

- In principle, nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered for allergic reactions immediately after the administration of NSAIDs
- Morphine and codeine should not be administered if the patient is allergic to them.
Other opioids may be administered

Chemical classification of nonsteroidal anti-inflammatory drugs

Chemical group	Drugs
Salicylic acid	Aspirin, salicylic acid, difunisal
Carbo/hetero acetic acid	Indomethacin, aceclofenac, sulindac, ketorolac, etodolac, tolmetin
Phenyl acetic acid	Diclofenac, aceclofenac
Propionic acid	Ibuprofen, naproxen, loxoprofen, ketoprofen, dexketoprofen
Enolic acid	Meloxicam, piroxicam, tenoxicam
Fenamic acid	Mefenamic acid, floctafenine
Pyridinic sulfonamide	Nimesulide
Naphyl alkanone	Nabumetone
Diaryl heterocyclic	
▪ with sulfone group	Etoricoxib
▪ with sulfa group	Celecoxib, parecoxib, valdecoxib

Modified from Blanca-Lopez N, Somoza-Alvarez ML, Bellon T, Amo G, Canto G, Blanca M. NSAIDs hypersensitivity: questions not resolved. Curr Opin Allergy Clin Immunol. 2018 Aug;18(4):291-301. doi: 10.1097/ACI.0000000000000454.

Opioid subclasses

```
graph TD; A[Opioid subclasses] --> B[Phenanthrenes]; A --> C[Phenylpiperidines]; A --> D[Diphenylheptanes]; B --- B_list["• Morphine<br>• Codeine<br>• Pethidine"]; C --- C_list["• Fentanyl<br>• Alfentanil<br>• Remifentanyl<br>• Sufentanil<br>• Meperidine"]; D --- D_list["• Methadone<br>• Propoxyphene"];
```

Phenanthrenes

- Morphine
- Codeine
- Pethidine

Phenylpiperidines

- Fentanyl
- Alfentanil
- Remifentanyl
- Sufentanil
- Meperidine

Diphenylheptanes

- Methadone
- Propoxyphene

PERIOPERATIVE DIAGNOSIS

- **Timing of onset**
- **Clinical presentation**
- **Criteria for diagnosis and severity classification**
- **Risk factors**
- **Laboratories**
- **Differential diagnosis**



PERIOPERATIVE DIAGNOSIS

Timing of onset

- 90% of perioperative anaphylaxes develop during anesthesia induction
- May develop within seconds or minutes of exposure and worsen rapidly



CLINICAL PRESENTATION



Mucocutaneous

Urticaria, angioedema



Respiratory

Wheez, stridor, dyspnea



Digestive

Nausea, vomiting,
diarrhea, cramping



Cardiovascular

Collapse, palpitation

Table 1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (over minutes to several hours) with involvement of the skin, mucosa, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
 - a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (within minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., cramping abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (within minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

PEF, peak expiratory flow; BP, blood pressure

*Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 X age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years

Modified from Sampson et al. [25]

Table 2 Clinical symptoms for diagnosing anaphylaxis during anesthesia

Symptom type	Objective findings	Subjective findings
Cardiovascular	Sudden decrease in blood pressure, tachycardia > bradycardia, arrhythmia	Collapse, palpitation, anterior chest pain
Respiratory	Wheezing/bronchospasm, findings of airway narrowing on capnometer, decrease in tidal volume during pressure-controlled ventilation, increase in maximal airway pressure during volume-controlled ventilation, hypoxemia associated with the above (decrease in SpO ₂ and/or PaO ₂)	Hoarseness, laryngeal strangulation, wheezing, dyspnea, respiratory arrest
Mucocutaneous	Flushing, erythema, angioedema, morbilliform, erythema around the eyelids, edema, conjunctival erythema, tears, edema of the lips, tongue, and palate	Itchy skin
Digestive organ	Not applicable	Persistent colic attacks, vomiting
Central nervous system	Not applicable	Unconsciousness, coma, convulsions
Others	Not applicable	Syncope, incontinence

Created based on [22, 26–28]

TABLE 2**Severity scale for classification of anaphylactic reactions**

Grade	Skin and subjective generalized symptoms	Abdomen	Respiratory tract	Cardiovascular
I	Itching Flushing Urticaria Angioedema	–	–	–
II	Itching Flushing Urticaria Angioedema	Nausea Cramps Vomiting	Rhinorrhea Hoarseness Dyspnea	Tachycardia (rise >20/min) Hypotension (fall >20 mm Hg systolic) Arrhythmia
III	Itching Flushing Urticaria Angioedema	Vomiting Diarrhea	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Itching Flushing Urticaria Angioedema	Vomiting Diarrhea	Respiratory arrest	Cardiovascular arrest

(Modified from Ring and Messmer 1977 [4]); flushing = sudden erythema

PERIOPERATIVE DIAGNOSIS

Identification of the causative substance

- Muscle relaxants
- Antibacterial agents
- Latex
- Chlorhexidine
- Intravenous anesthetics
- Opioids
- Colloid fluids

PERIOPERATIVE DIAGNOSIS

Risk factors for anaphylaxis

- Female sex
- History of anaphylaxis
- History of drug allergies
- Asthma
- History of frequent surgery
- Diseases caused by mast cell abnormalities

PERIOPERATIVE DIAGNOSIS

Laboratories finding

- Plasma tryptase
- Histamine levels

Differential diagnosis

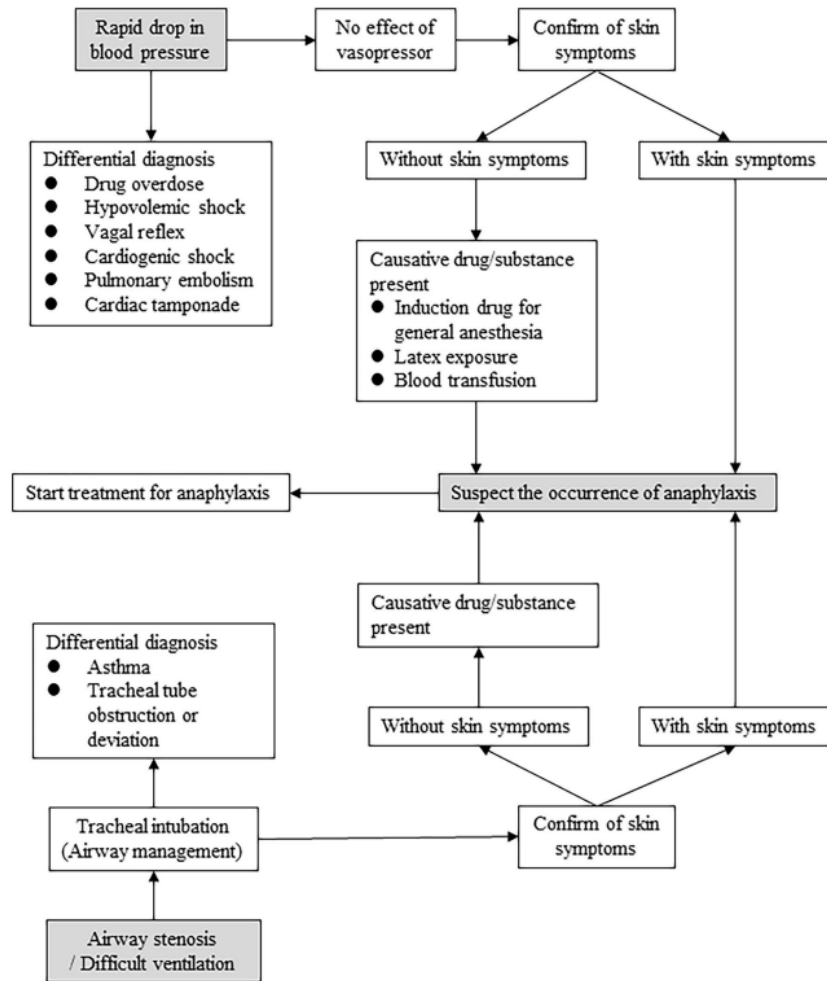
Table 3 Differential diagnosis

	Pathology to be differentiated	Points for differentiation
During general anesthesia		
Low blood pressure	Hemorrhagic shock	None of them have the skin symptoms characteristic of anaphylaxis, and neither do they respond to the corresponding treatment. However, urticaria develops in allergic acute coronary syndrome during anaphylactic shock
	Cardiogenic shock (myocardial infarction, myocardial ischemia, arrhythmia)	
	Pulmonary embolism	
	Cardiac tamponade	
	Tension pneumothorax	
	Hypovolemic shock	
	Hypotension due to intravenous anesthetics during induction	
	Drug overdose	
	Vagal reflex	
	Pulmonary edema	
Sepsis	Sepsis	Sudden redness of the skin develops and lasts for a few seconds to 30 min. When anesthesia is the trigger, symptoms persist for a long time and blood pressure decreases. Somatostatin is highly effective
	Carcinoid syndrome	
Bronchial spasm	Asthma attack	Usually, no skin symptoms or hypotension
	Tracheal tube trouble (obstruction, deviation)	There are usually no skin symptoms. It is important to ensure that the airway is secured by auscultation and bronchoscopy
Skin flushing, redness	Redman syndrome	Rapid administration of vancomycin
	Mast cell hyperplasia	Endogenous histamine excess. Opioids, NSAIDs, vancomycin, muscle relaxants, etc. may be triggers
During local anesthesia		
Flushing, dyspnea	Anxiety/panic attacks	Urticaria, angioedema, wheezing, and hypotension do not occur
	Autonomic epilepsy	Associated with epileptic seizures
	Hereditary angioedema (C1 inhibitory factor deficiency)	No itching or urticaria. nausea, vomiting, abdominal pain, dyspnea due to airway edema



04

TREATMENT



Rapid drop in blood pressure

No effect of vasopressor

Confirm of skin symptoms

Differential diagnosis

- Drug overdose
- Hypovolemic shock
- Vagal reflex
- Cardiogenic shock
- Pulmonary embolism
- Cardiac tamponade

Without skin symptoms

Causative drug/substance present

- Induction drug for general anesthesia
- Latex exposure
- Blood transfusion

With skin symptoms

Start treatment for anaphylaxis

Suspect the occurrence of anaphylaxis

Differential diagnosis

- Asthma
- Tracheal tube obstruction or deviation

Causative drug/substance present

Without skin symptoms

With skin symptoms

Tracheal intubation
(Airway management)

Confirm of skin symptoms

Airway stenosis / Difficult ventilation

TREATMENT

- Discontinue the use of all possible causative drugs
- Gather help to record the clinical course and treatment details of the patient
- Raise the patient's legs from the supine position
- Administer oxygen via a mask (6–8 L/min) or 100% oxygen if the patient is intubated
- Secure a venous route if it has not been done

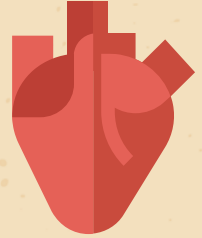
TREATMENT

- Administer adrenaline
 - Start continuous intravenous infusion if repeat doses are needed (low pressure: administer 0.2 µg/kg intravenously; circulatory collapse: administer 0.05–0.3 mg intravenously)
 - If a venous route is not available, administer 0.3 mg as an intramuscular injection (0.01 mg/kg for children)
- Perform tracheal intubation if laryngeal/pharyngeal edema progresses
- Ensure crystalloid fluid replenishment (until recovery of blood pressure)
 - 5–10 mg/kg during the first 5 min
 - 30 mL/kg for children during the first hour

TREATMENT

- Second – line treatments
 - Bronchodilators
 - Corticosteroid preparations
 - Adult: Hydrocortisone 200 mg
 - Children 12 years or older: Hydrocortisone 200 mg
 - 6–12 years old: Hydrocortisone 100 mg
 - 6 months to 6 years old: Hydrocortisone 50 mg
 - Antihistamines
 - Cardiovascular agonists

Kounis syndrome



- Condition in which an allergic reaction and acute coronary syndrome occur simultaneously
 - Histamine has a coronary artery spasm effect
 - Tryptase and chymase destabilize coronary artery plaques
- Treatment for anaphylaxis and acute coronary syndrome should be performed at the same time

POSTOPERATIVE DIAGNOSIS

In vivo testing

- Skin test
 - Prick test
 - Intradermal test
- Challenge test
- Patch test

POSTOPERATIVE DIAGNOSIS

In vitro testing

- BAT
- Histamine release test(HRT)
- Measurement of tryptase and histamine
- Measurement of allergen-specific IgE

TAKE HOME MESSAGE



- Perioperative anaphylaxis is a life-threatening immediate hypersensitivity reaction that is usually IgE-mediated
- Antibiotics and neuromuscular blocking agents are the most common triggers
- The Ring and Messmer four step (I-IV) grading scale is the most widely accepted tool for describing the clinical severity
- The most common clinical presentation includes cardiovascular collapse, tachycardia and cutaneous features (Grade III)
- The cornerstones of management are adrenaline (epinephrine) and i.v. fluids
- Diagnosis is based on the clinical presentation, in conjunction with mast cell tryptase concentrations and the results of skin testing



Thank you

REFERENCES



- P. Dewachter and L. Savic. Perioperative anaphylaxis: pathophysiology, clinical presentation and management. BJA Education, 19(10): 313-320 (2019)
- Tomonori Takazawa. Practical guidelines for the response to perioperative anaphylaxis. Journal of Anesthesia. 14 October 2021. <https://doi.org/10.1007/s00540-021-03005-8>
- Pascale Dewachter. Anaphylaxis and Anesthesia Controversies and New Insights. Anesthesiology 2009; 111:1141–50
- Duminda N. Wijeyesundera and Emily Finlayson. Preoperative Evaluation. Miller RD, editors, Miller's Anesthesia nine edition. Philadelphia: PA; 2020. p.918-98