ANAFILAXIA

ANAFILAXIA

- Reprezinta o urgenta medicala, ce necesita diagnostic si interventie terapeutica rapida
- Constituie un sindrom multi-sistemic, survenit consecutiv eliberarii de mediatori de la nivelul mastocitelor si bazofilelor
- Cel mai frecvent apare consecutiv reactiilor imunologice induse de alimente, medicamente, muscaturi de insecte etc sau nonimunologice, produse de orice agent ce poate determina degranularea masiva si rapida a mastocitelor sau bazofilelor

ANAFILAXIA

Mecanismul implicat in cele mai multe cazuri implica contributia Ig E.

Termenul de ”anafilaxie” a fost atribiut clasic evenimentelor IgE dependente, iar cel de “reactie anafilactoida” celor independente de contributia IgE, desi, clinic, cele doua tipuri de reactii **nu** se pot delimita.

WAO (Organizatia Mondiala a Alergiilor) clasifica anafilaxia ca fiind imunologica sau nonimunologica

ANAFILAXIA

- ***Anafilaxia imunologica***– include:
  - reactiile mediate de IgE
  - reactiile mediate de IgG-neidentificate la specia umana
  - Ireactiile mediate de formarea complexelor imune

- ***Anafilaxia nonimunologica*** –determinata de orice agent ce poate induce degranularea brusca si masiva a mastocitelor si bazofilelor in absenta interventiei imunoglobulinelor

ANAFILAXIA

Anafilaxia imun mediata

IgE-mediata —mecanismul clasic asociatreactiei alergice este initiat de interactiunea dintre antigen (alergen) si IgE legata de receptorul Fc-epsilon-RI de la nivelul mastocitelor si/sau bazofilelor

Mediata de complexe imune— exista multiple medicamente asociate reactiilor alergice similare anafilaxiei, fara a putea fi identificata IgE specifica preparatului respectiv.

ANAFILAXIA

Anafilaxia imunologica

IgG-mediata— nu a fost demonstrata la specia umana, ci doar in studii experimentale

Alte medicanisme— exista multiple mecanisme, non IgE mediate, au fost dovedite a fi implicate in anafilaxia determinata de agenti de contrast radiologici
-unul dintre acestea consta in interactiunea moleculelor agentului de contrast cu portiunea Fc a IgE sau IgG legat de Ma sau Ba→reactie incrucisata si activare.

ANAFILAXIA

Anafilaxia non imunologica

Mecanisme potentiale:

- **Activarea complementului**, in absenta formarii de complexe imune

Unele celule mastocitare exprima pe suprafata receptori pentru anafilatoxinele C3a si C5a, si determina eliberarea histaminei ca raspuns la expunerea la fragmentele complementului
Receptorii pentru C3a sunt localizati si la nivelul Ma si Ba si pot produce PAF, consecutiv activarii
Ex. propofol

ANAFILAXIA

Anafilaxia non imunologica

- **Activarea directa a Ma si/sau Ba** de catre vancomicina→eliberarea de histamina→sindromul "red man"
  -reactia este asociata cu hTA si poate avea expresie clinica similara anafilaxiei

- Opioidele, de ex. Meperidina si codeina, pot determina **eliberarea directa a histaminei**, prin degranulare mastocitara

Reactiile usoare, urticariene, sunt frecvent sesizate

ANAFILAXIA

Anafilaxia non imunologica

- Urticaria indusa de expunerea la frig consta in aparitia rapida a eritemului, pruritului si edemului; expunerea poate fi consecutiva expunerii la temperaturi scazute, apa/bauturi reci sau orice alta sursa de temperatura joasa.
- Reactia este consecutiva eliberarii masive de histamina si alti mediatori→hTA

ANAFILAXIA

Mediatori eliberati in cursul reactiei anafilactice

Consecutiv activarii si degranularii, Ma si Ba elibereaza mediatori preformati, cei mai importanti fiind *histamina si triptaza,* detectati relativ rapid atat seric, cat si urinar la scurt timp dupa debutul simptomatologiei

FORME CLINICE

- cel mai frecvent, simptomele survin si se intensifica progresiv, cu rezolutie ulterioara
- reactia anafilactica bifazica consta in recurenta simptomatologiei dupa aparenta rezolutie a acestora, fara expunere ulterioara la factorul declansator
- anafilaxia prelungita-dureaza ore, zile sau chiar saptamani, in cazuri extreme

SIMPTOMATOLOGIE CLINICA

- Afectarea sistemica implica, cel mai frecvent, afectare cardiaca, vasculara si respiratorie, decesul survenind consecutiv colapsului ciruclator sau respirator
- **Semne si simptome:**
- **Cutanate:** flush, prurit, edem, piloerectie
- Edem lingual, labial, gust metalic
- Respirator:
  - prurit, congestie nazala, rinoree, disfonie, stridor, edem laringeal,
  - Tuse, dispnee, cianoza

- **Gastroinetstinale:** greata, varsaturi, dureri abdominale, diaree..
- **Cardiovascular:** dureri precordiale, bradi/tahicardie sau alte tipuri de aritmii, hTA, sincopa, colaps
- **Neurologice:** cefalee, anxietate, confuzie, crize convulsive, tulburari de comportament
- **Oculare:** hiperemie conjunctivala, edem periorbital, prurit

Symptoms and signs of anaphylaxis

Skin
Feeling of warmth, flushing (erythema), itching, urticaria, angioedema, and "hair standing on end" (pilor erection)
Oral
Itching or tingling of lips, tongue, or palate
Edema of lips, tongue, uvula, metallic taste
Respiratory
Nose - Itching, congestion, rhinorrhea, and sneezing
Laryngeal - Itching and "tightness" in the throat, dysphonia, hoarseness, stridor
Lower airways - Shortness of breath (dyspnea), chest tightness, cough, wheezing, and cyanosis

Gastrointestinal
Nausea, abdominal pain, vomiting, diarrhea, and dysphagia (difficulty swallowing)
Cardiovascular
Feeling of faintness or dizziness; syncope, altered mental status, chest pain, palpitations, tachycardia, bradycardia or other dysrhythmia, hypotension, tunnel vision, difficulty hearing, urinary or fecal incontinence, and cardiac arrest
Neurologic
Anxiety, apprehension, sense of impending doom, seizures, headache and confusion; young children may have sudden behavioral changes (cling, cry, become irritable, cease to play)
Ocular
Periorbital itching, erythema and edema, tearing, and conjunctival erythema
Other
Uterine cramps in women and girls

Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
B. Reduced BP* or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)
2. TWO OR MORE OF THE FOLLOWING that occur rapidly *after exposure to a LIKELY allergen for that patient* (minutes to several hours):
A. Involvement of the skin mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
C. Reduced BP* or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)
D. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP* *after exposure to a KNOWN allergen for that patient* (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

- **EXPLORARI PARACLINICE—** se pot determina:
- triptaza (ser/plasma)
- histamina (plasma, urina)
- N-metil-histamina (plasma, urina)
- 11-beta-PGF
- 2-alpha (ser/plasma, urina)
- LTE (urina)
- metabolitul histaminei, acidul acetic n-metil-imidazole (urina)
- PAF, PGD2, chimaza...

- total tryptase, produced by mast cells and basophils, should ideally be measured 30 to 120 minutes after the onset of anaphylaxis signs or symptoms, ideally from one to two hours after onset, because most patients have recovered from hypotension by one hour and levels should be at or near peak during the second hour after onset
- histamine elevations are even more fleeting.
- plasma histamine levels peak within 5 to 10minutes after symptom onset and decline with a half-life of 1 to 2 minutes, such that levels typically return to baseline by 15 to 30 minutes; therefore, samples should be drawn as soon as possible, preferably 2 to 15 minutes from the onset of symptoms

Differential diagnosis of anaphylaxis

Common disorders
Acute generalized urticaria and/or angioedema*
Acute asthma exacerbation*
Vasovagal syncope (faint)
Panic attack/acute anxiety attack
Other respiratory events
Pulmonary embolism
Pneumothorax
Foreign body aspiration (especially in children)
Vocal cord dysfunction
Epiglottitis
Hyperventilation

Cardiac events
Myocardial infarction*
Dysrhythmia
Acute symptoms related to structural disorders (eg, aortic stenosis, hypertrophic cardiomyopathy)
Shock
Hypovolemic¶ (eg, gastrointestinal bleed, ruptured ectopic pregnancy, ruptured aortic aneurism, systemic capillary leak syndrome)
Cardiogenic
Distributive¶ (eg, sepsis, spinal cord injury)
Obstructive (eg, pulmonary embolism, tension pneumothorax, cardiac tamponade)
Flushing
Perimenopause
Carcinoid syndrome
Autonomic epilepsy
Medications
Alcohol
Medullary carcinoma of the thyroid
Red man syndrome (vancomycin)

Postprandial syndromes
Scombroidosis
Anisakiasis
Pollen-food allergy syndrome
Food poisoning
Caustic ingestion (especially in children)
Neurologic events
Seizure
Cerebrovascular event (stroke)
Nonorganic disease
Munchausen syndrome
Psychosomatic episode

TRATAMENT

- Indepartarea cauzei, atunci cand este posibila
- Administrarea im a epinefrinei, daca este disponibila
- Plasarea p[acientului in pozitie de supinatie, cu elevarea membrelor inferioare
- Administrarea de oxigen suplimentar
- Administrarea de fluide iv

- **EPINEFRINA INTRAMUSCULARA)**
- Este alegerea de electie pentru managementul initial al reactiei anafilactice
- Administrarea im injection iofera o concentratie plasmatica maxima mai rapida comparativ cu cea sc
- Administrarea iv poate determina complicatii cardiovasculare
- **Fiole pentru administrare im 1 mg/ml** (1:1000)
- **Doza im** – atunci cand este posibila dozarea exacta, la orice varsta, 0.01 mg/kg (maxim 0.5mg) pentru o administrare, inj in partea medie si laterala a coapsei-muschiul vast lateral

- Doza de. 0.1 mg poate fi administrata cu ajutorul injectomatului sau prin administrarea a 0.1 ml din solutia de 1 mg/ml
- Nou nascut sau copii cu greutatea intre 10 kg -25 kg: 0.15 mg
- Pacienti >25 pana la 50 kg -0.3 mg
- >50 kg- 0.5 mg

- in cele mai multe cazuri o singura administrare este suficienta pentru rezolutia simptomatologiei
- Administrarea poate fi repetata la intervale de 5-15 minute in absenta raspunsului sau a unui raspuns insuficient
- La pacientii cu hTA persistenta, este recomandata administrarea de fludie iv
- In cazul persistentei simptomatologiei severe, se va administra epinefrina iv, in bolus, 0.05-0.1 mg, cu monitorizarea parametrilor hemodinamici

- **Administrarea epinefrinei in perfuzie iv continua**
- Este indicata in cazurile non responsive la administrarea repetata im asociata fluidelor iv
- 10ml de solutie preumpluta 0.1 mg/ml (1 mg) in 1000 ml solutie salina
- 1 mcg/minut pentru fiecare 60 ml/h de solutie→ 120 ml/h-2 mcg/minute samd
- La pacientii la care s-au administrat deja cantitati mari de fludie iv, este preferata administrarea unei solutii de 4mcg/ml
- administrarea iv a epinefrinei se incepe cu o rata de **0.1 mcg/kg/minut** si se creste la fiecare 2-3 minute cu 0.05 mcg/kg/minut pana la obtinerea unei TA in limite

- Actiunea terapeutica a epinefirnei este consecutiva:
- **Efectelor alpha-1-adrenergic** – vasoconstrictie→ cresterea RVP, a TA, remiterea edemului mucoaselor
- **Efecte agoniste beta-1-adrenergice**– inotrop, cronotrop pozitiv.
- **Efecte agoniste beta-2-adrenergice**– bronhodilatatie si scaderea eliberarii de mediatori inflamatori de la nivelul Ma si Ba

- **EFECTE ADVERSE**
- Uneori anxietate, cefalee, ameteala, palpitatii, tremor
- Rareori aritmii ventriculare, angina pectorala, infarct miocardic, edem pulmonar, cresterea rapida a TA, hemoragii intracraniene

CONTRAINDICATII-nu exista contraindicatii absolute pentru administrarea epinefrinei

- **GLUCAGON**
- Terapia beta-blocanta cu/fara IECA asociat poate determina reactii anafilactice extrem de severe
- Administrarea glucagonului, 1-5mg iv lent, urmat de administrarea perfuzabila, cu un ritm de 5-15mcg/minut, poate fi indicata la pacientii refractari la administrarea de epinefrina

- **AGENTI ADJUVANTI**— antihistaminice, bronhodilatatoare, GC...

- **ALTE VASOPRESOARE**— dopamina...

Comorbidities and concurrent medications that might impact the severity and treatment of anaphylaxis

Comorbidities
Asthma
Other pulmonary diseases (eg, COPD, interstitial lung disease)
Cardiovascular diseases (eg, ischemic heart disease, hypertensive vascular disease, cardiomyopathy)
Mast cell disorder (ie, systemic mastocytosis or mast cell activation syndrome)
Concurrently administered medications
Beta-adrenergic blockers*
Alpha-adrenergic blockers¶
Angiotensin-converting enzyme (ACE) inhibitorsΔ
Angiotensin II receptor blockersΔ
Tricyclic antidepressants$\diamond$
Monoamine oxidase inhibitors§
ADHD medications¥ (eg, stimulants, such as methylphenidate and amphetamines)
Recreational use of cocaine‡

COPD: chronic obstructive pulmonary disease; ADHD: attention deficit hyperactivity disorder.

* Beta-adrenergic blockers, administered orally or topically (eg, eye drops) may be associated with severe anaphylaxis and may also make anaphylaxis more difficult to treat by causing unopposed alpha-adrenergic effects, hypertension, and reduced bronchodilator response to the beta-adrenergic effects of endogenous or exogenous epinephrine.

¶ Alpha-adrenergic blockers may decrease the effects of endogenous or exogenous epinephrine at alpha-adrenergic receptors, potentially making patients less responsive to the alpha-adrenergic effects of epinephrine.

Δ Potential interference with endogenous compensatory responses.

$\diamond$ Potential increase in adverse effects of epinephrine because of prevention of epinephrine uptake at adrenergic receptors.

§ Potentiate epinephrine's effects by inhibiting its metabolism by monoamine oxidase.

¥ Side effects are similar to those of epinephrine.

‡ Potentiates epinephrine's effects, especially cardiovascular effects, by preventing its reuptake into adrenergic neurons.

Modified with permission from: Simons FER. Anaphylaxis, killer allergy: Long-term management in the community. J Allergy Clin Immunol 2006; 117:367. Copyright © 2006 Elsevier.

Gell and Coombs classification of immunologic drug reactions

Type	Description	Mechanism	Clinical features
I Immediate reaction (within one hour)	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances, such as histamine, prostaglandins, and leukotrienes.	Anaphylaxis Angioedema Bronchospasm Urticaria (hives) Hypotension
II	Antibody-dependent cytotoxicity	An antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement activation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (ie, types IVa to IVd).	Contact dermatitis Some morbilliform reactions Severe exfoliative dermatoses (eg, SJS/TEN) AGEP DRESS/DiHS Interstitial nephritis Drug-induced hepatitis Other presentations

IgE: immunoglobulin E; Fc IgG: Fc portion of immunoglobulin G; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis; DRESS/DiHS: drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.

Adapted from: Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515.

UpToDate®