Anaphylaxis

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Definition

EAACI

A serious, life-threatening, generalized or systemic **hypersensitivity** reaction

(objective recurrent symptoms after well tolerate stimulus by healthy persons)

Johansson SGO. Allergy 2001; 56: 813-824

Serious allergic reaction that is rapid in onset and might cause death;
Low blood pressure is not necessary for recognition

Simons FER. JACI 2010; 125: s161-181

Examples of risk- and co-factors of anaphylaxis

Lifestyle factors	• physical exertion • alcohol
Drugs	• NSAIDs • ACE inhibitors • β-blockers
Patient-specific factors	• adolescence, advanced age and sex • infections • hormonal status • psychogenic stress
Pre-existing conditions	• asthma and other IgE dependent diseases • cardiovascular disease • mastocytosis and/or increased basal tryptase

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, 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 peak expiratory flow (PEF), hypoxemia)

   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

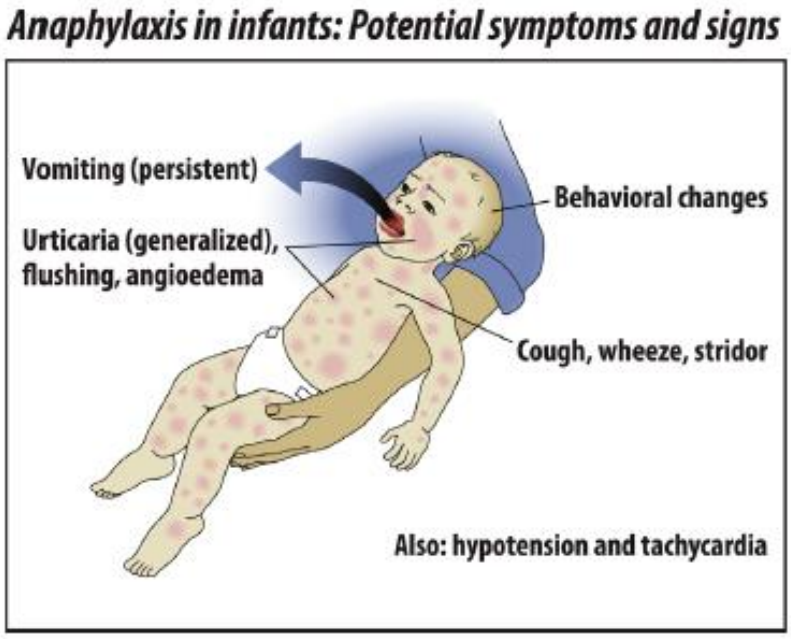
Sampson HA. *JACI* 2006;117:391-397

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 (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., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to 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 mm Hg or greater than 30% decrease from that person's baseline

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

Anaphylaxis in infants



Simons *JACI* 2015; 135:1125

Anaphylaxis recognition

BASED ON SYMPTOMES

- Laboratory tests – non-specific:
- **Serum tryptase** in serum 15 min - 3 h form starting symptomes – serum – 1 year (-) 20^0C
- **Histamin** – in serum – 15-60 minut – e.g. – elevated also in scombrioidosis

- Diagnostic tests 3-4 weeks after episode

Differential diagnosis

Skin or mucosal	• chronic remittent or physical urticaria and angioedema • pollen-food syndrome
Respiratory diseases	• acute laryngotracheitis • tracheal or bronchial obstruction (e.g. foreign substances, vocal cord dysfunction) • status asthmaticus (without involvement of other organs)
Cardiovascular diseases	• vasovagal syncope • pulmonary embolism • myocardial infarction • cardiac arrhythmias • hypertensive crisis • cardiogenic shock
Pharmacological or toxic reactions	• ethanol • histamine (e.g. scombroid fish poisoning) • opiates

Differential diagnosis

Neuropsychiatric diseases	• hyperventilation syndrome • anxiety and panic disorder • somatoform disorder (e.g. psychogenic dyspnea, vocal cord dysfunction) • dissociative disorder and conversion (e.g. globus hystericus) • epilepsy • cerebrovascular event • psychoses • artifact (factitious disorder) • Hoigné's syndrome • coma (e.g. metabolic, traumatic)
Endocrinological diseases	• hypoglycemia • thyrotoxic crisis • carcinoid syndrome • vasointestinal polypeptide tumours • pheochromocytoma

Anaphylaxis vs. vaso-vagal reaction

V-V reaction	Anaphylaxis
Skin pale, sweat skin, cold	Skin redness, urticaria, pruritus
Bradykardia	Tachycardia
Prodromal symptomes: darkness before eyes, anxiety	
Quickly disappears (sec.)	

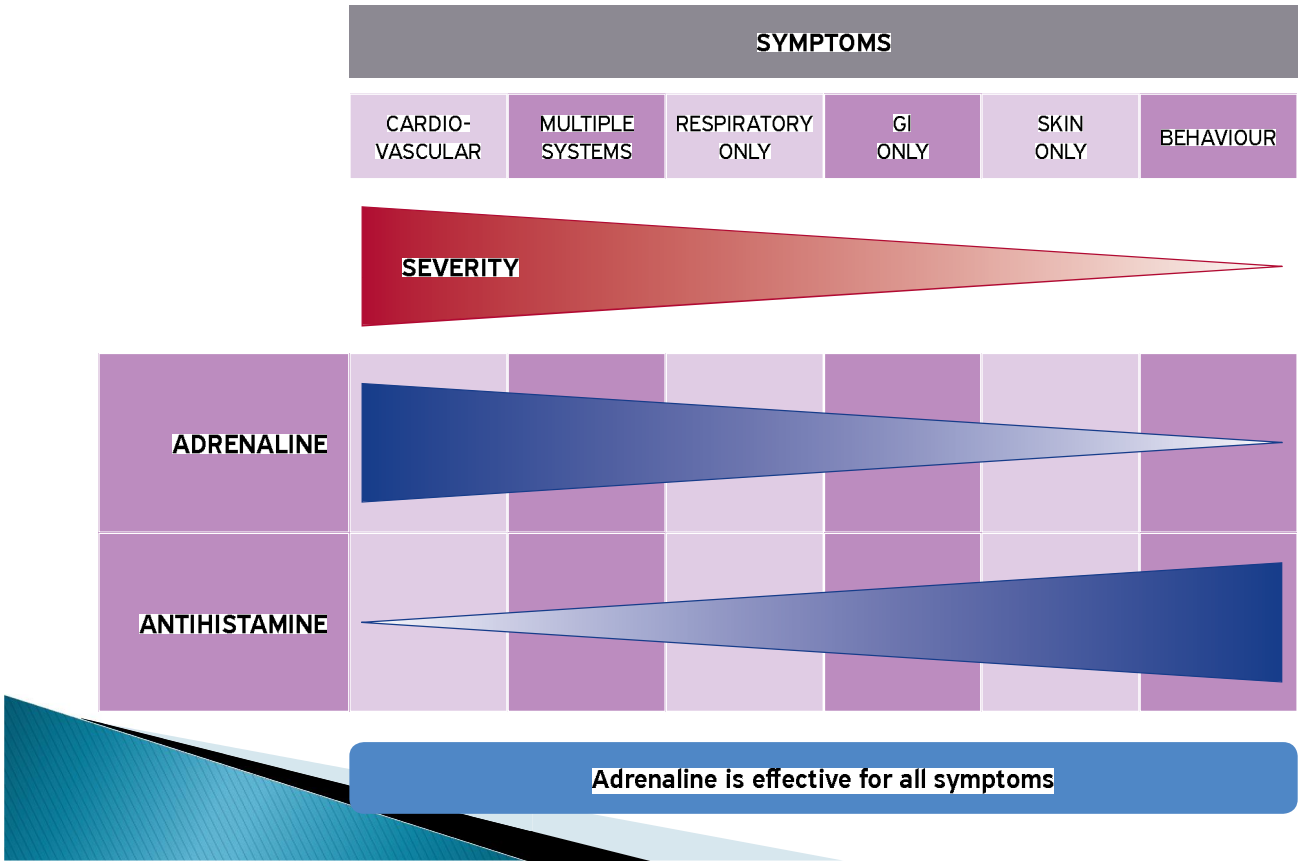
Anaphylaxis treatment

Drug of choice

- **EPINEPHRINE !!!!!!**

- II and III line drugs – dependence on symptomes;

Symptomes associated with anaphylaxis



Epinephrine - adverse effects

- Anxiety;
- Skin rush;
- Tremor;
- Dizziness;
- Headache;
- Lung oedema;
- Elevated BP;
- Acute coronary syndrome;
- Heart failure;
- Arrythmias;

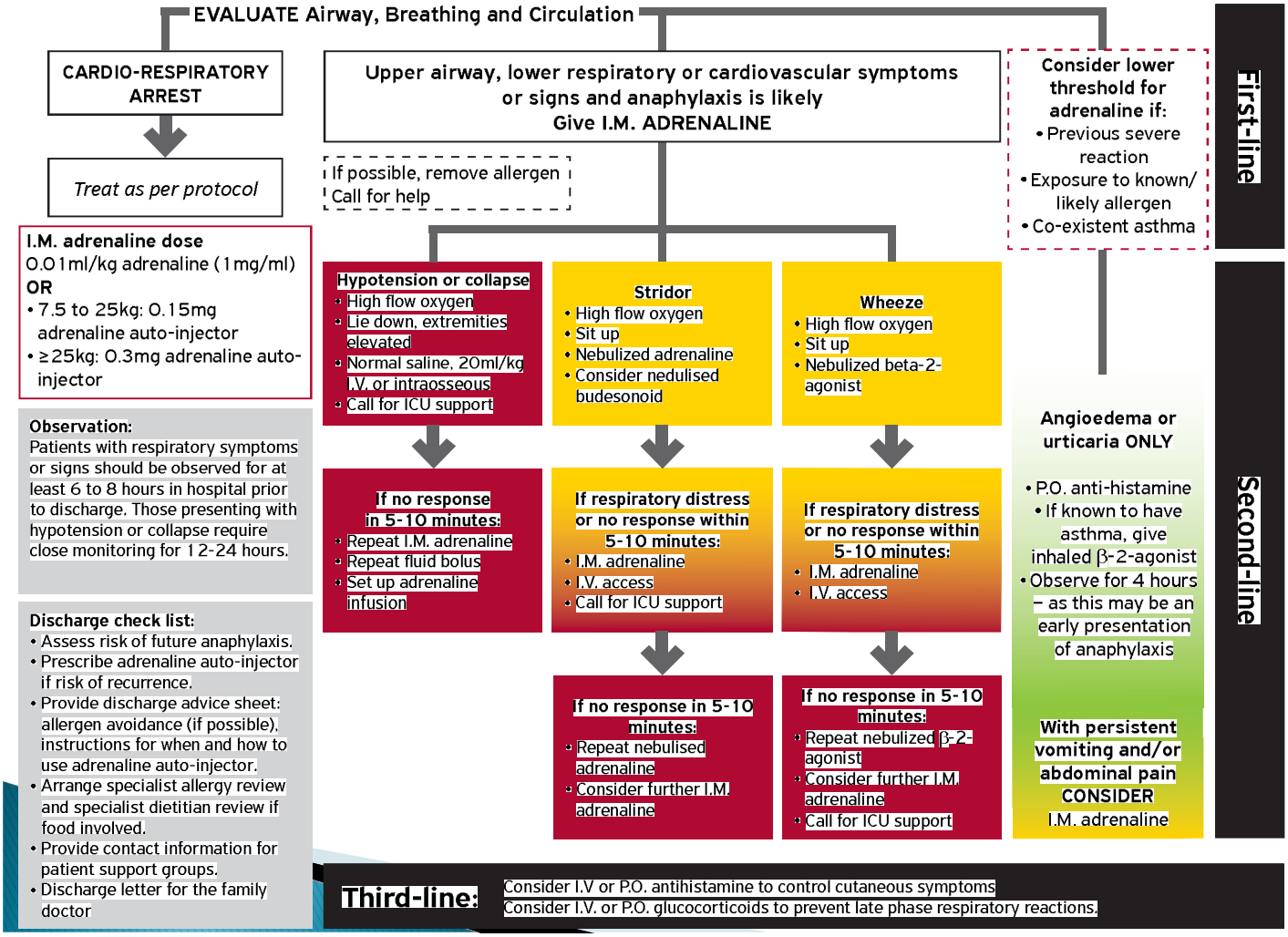
Proper dose was given

NOTICE ! Last three can be a part of anaphylaxis !!!!!

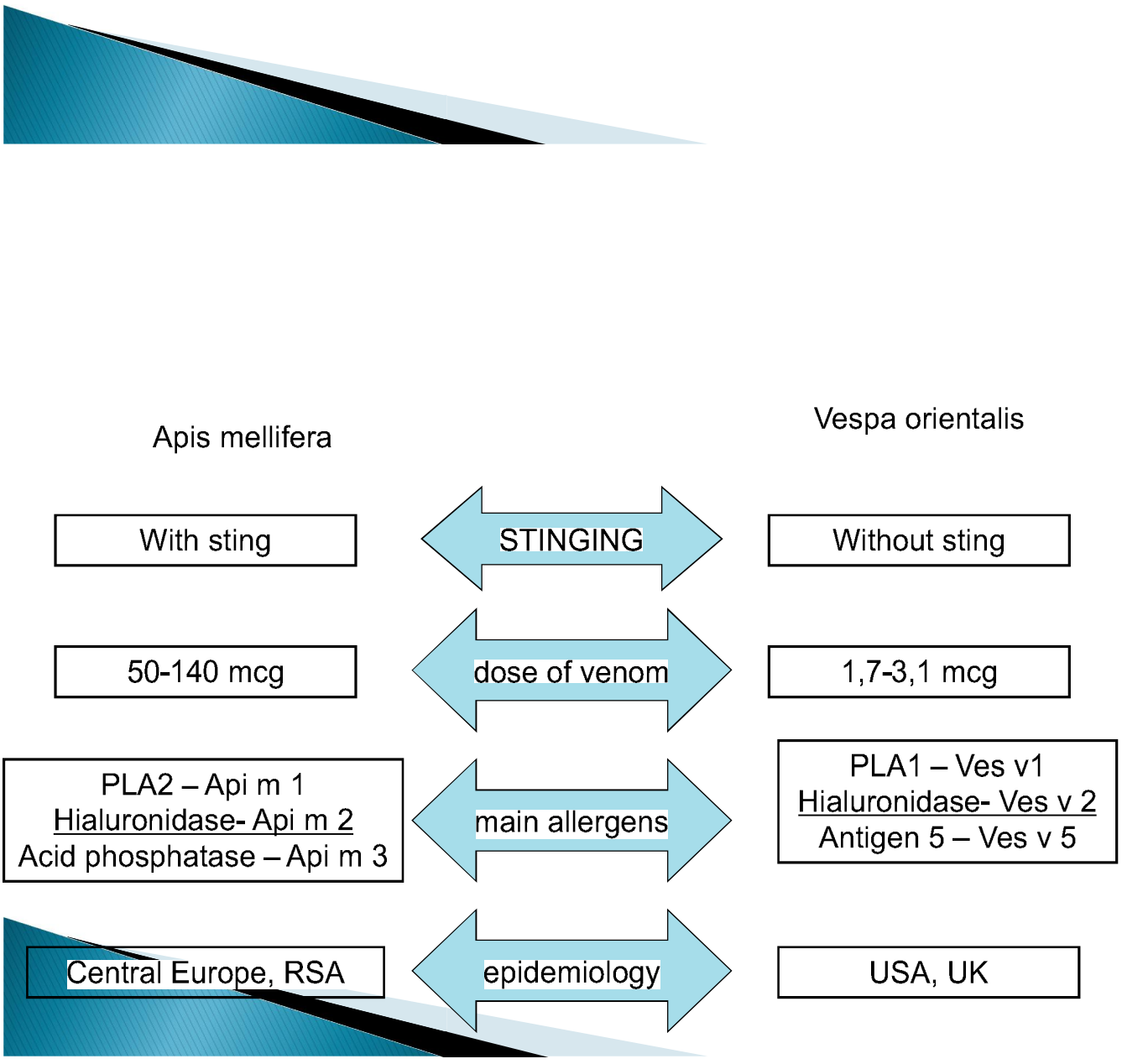
Checklist for managing anaphylaxis

1. Stay with patient
2. Look for signs of anaphylaxis
3. Administer adrenaline if signs of anaphylaxis
4. Repeat adrenaline as necessary
5. Other treatments as indicated (eg oxygen, beta-2 agonist, fluids, antihistamine, corticosteroid)
6. Look for trigger (eg food, drug, venom)

Adrenaline is effective for all symptoms



Hymenoptera allergy



Reactions

immunological

non-immunological

typical

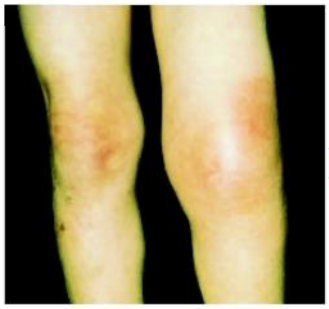
non-typical

Toxic reactions
e.g.
neurological
syndromes
hemolysis
death

IgE-mediated
LLR
urticaria
dyspnoe
anaphylactic shock

Typ III
Serum sickness
disease
G-B syndrome
Sch-H disease
Typ IV
myalgia

Local reactions



Large local reactions

Oedema in the sting place diameter **> 10 cm** and duration time **> 24 h;**

NOTICE: LLR reactions can be observed **2 - 7 days**, only few patients after next stinging present systemic reaction

No **diagnosis and specific immunotherapy** !!!!! (excl. recurrent LLR, diminished QoL)

Systemic reactions

Degree of reaction	Ring i Messmer classification	Müeller classification
I	Skin symptomes	urticaria, skin pruritus, weakness or anxiety
II	Mild to moderate systemic symptomes	angioedema, chest tightness, nausea, vomiting, diarrhoea, abdomen pain, dizziness
III	Anaphylactic shock, loss of consciousness	dyspnoe, wheezing, stridor, speach problems, hoarsness, weakness, confusing, fear of death
IV	Cardiac arrest	Low BP, loss of consciousness, incontinentia urinae and stool, cyanosis

Classification is based on the **most severe symptomes**
(none of the symptomes is obligatory)

Mild local reactions

- remove the sting
- wash the sting place with water and soap
- cold compress
- 24 to 48 h observe the place – secondary infections (especially after wasp stinging)
- no to to scratch – **secondary infections more probable**

Large local reactions

- AH orally
- **sGKS** – prednison – 1 mg/kg – 2-3 days

Treatment of systemic reaction to *Hymenoptera* sting

Type of reaction	Drug and dose	Notes
Mild urticaria	Antihistamines oral or parenteral	Observe for at least 60 minutes
Urticaria, angioedema	Check blood pressure and pulse rate Establish an i.v. line with saline Antihistamines oral or parenteral Corticosteroids oral or parenteral In case of severe or progressive symptoms: **Epinephrine** (1mg/ml): - Adults 0,30 – 0,50 mg i.m. - Children 0,01 ml/kg i.m.	Patient must be kept under observation until symptoms completely disappear

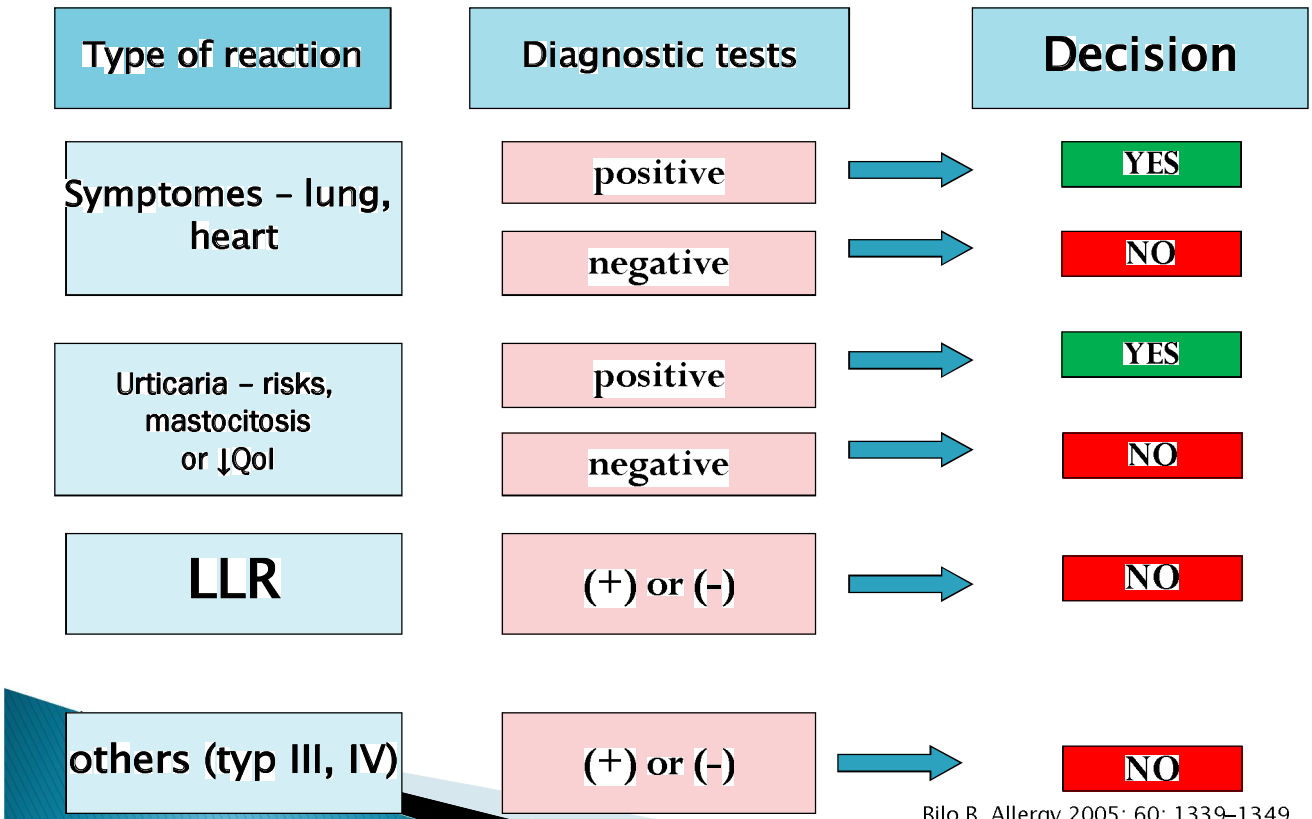
Treatment of systemic reaction to *Hymenoptera* sting

Type of reaction	Drug and dose	Notes
Laryngeal oedema	**Epinephrine** by inhalation or i.m.	Intubation, tracheotomy or cricothyrotomy may be needed in cases of more severe laryngeal oedema
Bronchial obstruction	Mild to moderate – beta2 –agonists by inhalation Severe - **Epinephrine** by inhalation beta2 –agonists (0,5 mg/ml) 1 year- 0,05 – 0,1 mg; 7 years- 0,2 - 0,4 mg; adults 0,25-0,5 mg	All patients with protracted respiratory symptoms must be hospitalized; those with laryngeal oedema must be given intensive medical care as soon as possible

Treatment of systemic reaction to *Hymenoptera* sting

Type of reaction	Drug and dose	Notes
Anaphylactic shock	**Epinephrine** (1mg/ml): - Adults 0,30 – 0,50 mg i.m. - Children 0,01 ml/kg i.m. May be repeated after 5-15 min. Exeptionally i.v. Place patient in supine position, oxygen 5-10 l/min Check blood pressure and pulse rate i.v.access, volume replacement (10-20 ml/kg 20 min) Antihistamines i.v. corticoids i.v.	Hospitalization necessary because of the risk of delayed anaphylaxis
	Dopamine or norepinephrine infusion	If epinephrine injections with or without antihistamines and volume expansion fail to alleviate hypotension
	Glucagone:0,1 mg/kg i.v (nausea, vomiting)	For refractory hypotension and bronchospasm in patients on beta-blokers

Indication for immunotherapy



Bilo B. Allergy 2005; 60: 1339–1349

Drug allergy

- Drug hypersensitivity reactions (DHRs) are adverse effects of drugs that clinically resemble allergic reactions.
- Drug allergies are DHRs for which a definite immunologic mechanism is demonstrated.
- For general communication, when a drug reaction is suspected, DHR is the preferred term.

Drug allergy

- Raported by parents – approx. 10%
- Viral infections as an important co-factors (ampicylin and EBV, HHV6 – DRESS)
- **Main drugs** : antibiotics especially beta-lactmas, NSAID, others antibiotics
- **Diagnosis** – the same in both – adults and children
- **IT** – painfull – in non-immediate reactions – drug provocation – diagnosis in the case of severe skin reactions

Reactions

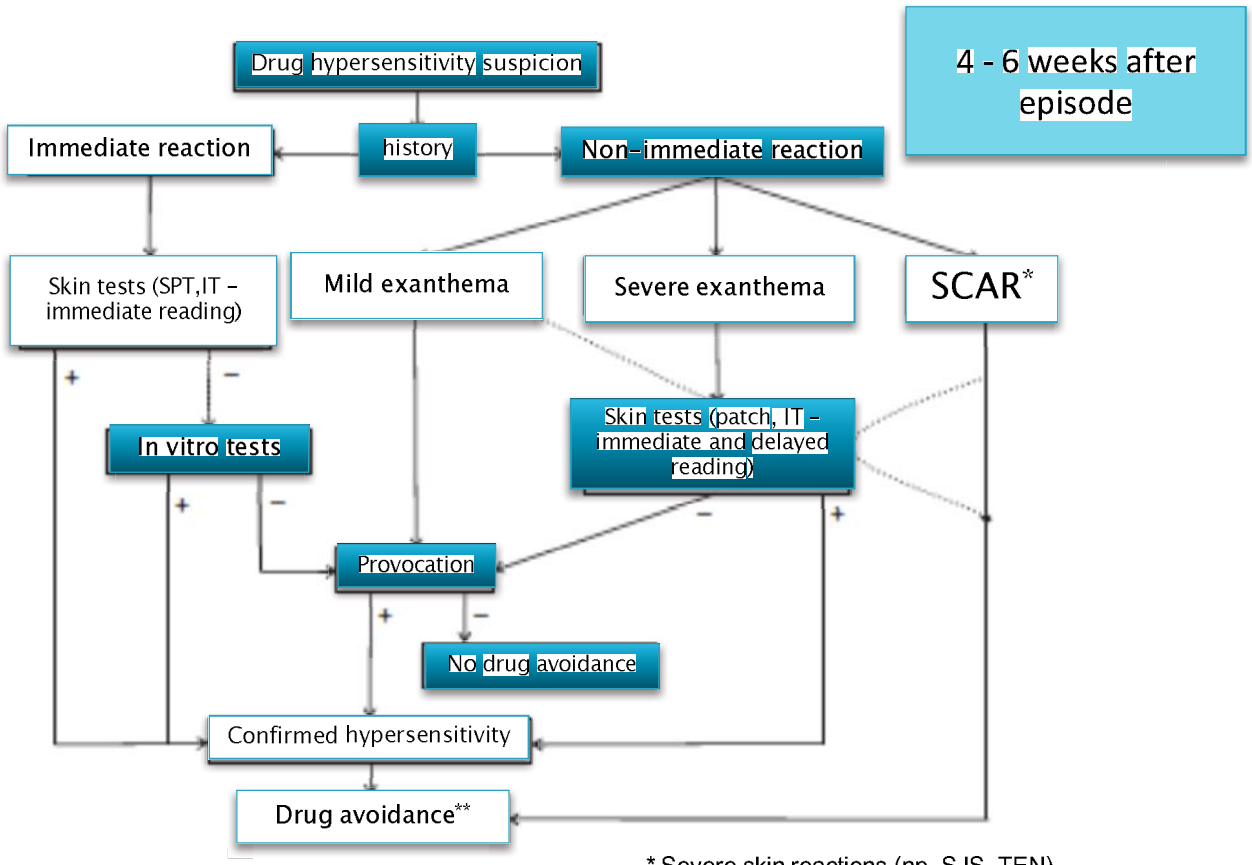
- **Immediate DHRs** – occur within 1-6 hours after the drug administration (typically within first hour)
- **Non-immediate DHRs –** usually after 6 (firts hour), even after 2- 5 days

Type	Type of immune response	Pathophysiology	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock, Angio-oedema, Urticaria, Bronchospasm	Within 1 to 6 hours after the last intake of the drug
II	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5-15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness, Urticaria, Vasculitis	7-8 days for serum sickness/ urticaria 7-21 days after the start of the eliciting drug for vasculitis
IVa	Th1 (IFNγ)	Monocytic inflammation	Eczema	1-21 days after the start of the eliciting drug
IVb	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculo-papular exanthema, DRESS	1 to several days after the start of the eliciting drug for MPE 2-6 weeks after the start of the eliciting drug for DRESS
IVc	Cytotoxic T-cells (perforin, granzyme B, FasL)	Keratinocyte death mediated by CD4 or CD8	Maculo-papular exanthema, SJS / TEN, pustular exanthema	1-2 days after the start of the eliciting drug for fixed drug eruption 4-28 days after the start of the eliciting drug for SJS / TEN
IVd	T-cells (IL-8/CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1-2 days after the start of the eliciting drug (but could be longer)

Diagnosis

- A **definitive diagnosis** of a DHR is in many cases required in order to institute proper preventive measures.
- Misclassification based on the DHR history alone may have consequences on individual treatment choices and be more detrimental for the patients than a **complete drug allergy work up**.
- The clinical tools allowing a definitive diagnosis include a **thorough clinical history, standardized skin tests, reliable in vitro tests** and **drug provocation tests**.
- **Screening** subjects without a prior history of allergic drug reactions **is not recommended**.

Drug allergy diagnosis



Drug desensitization

Desensitization should be considered when the offending drug is essential and when either no alternatives exist or they are unsatisfactory:

- Sulfonamides in HIV-infected patients.
- Quinolone allergies in some cystic fibrosis patients.
- Serious infections with allergy to ß-lactams, anti-tuberculosis drugs.
- Allergy to tetanus vaccine.
- Hemochromatosis with allergy to desferoxamine.
- Taxanes and platinum salt-based cancer chemotherapeutic agents.
- Monoclonal antibodies utilized in several types of hematological and non hematological neoplasms.

- Aspirin and NSAID hypersensitivity in patients for whom the necessity for these drugs to treat either a cardiac or rheumatic disease is clear.