Anaphylaxis

อ. พญ. ดารา ไม้เรียง

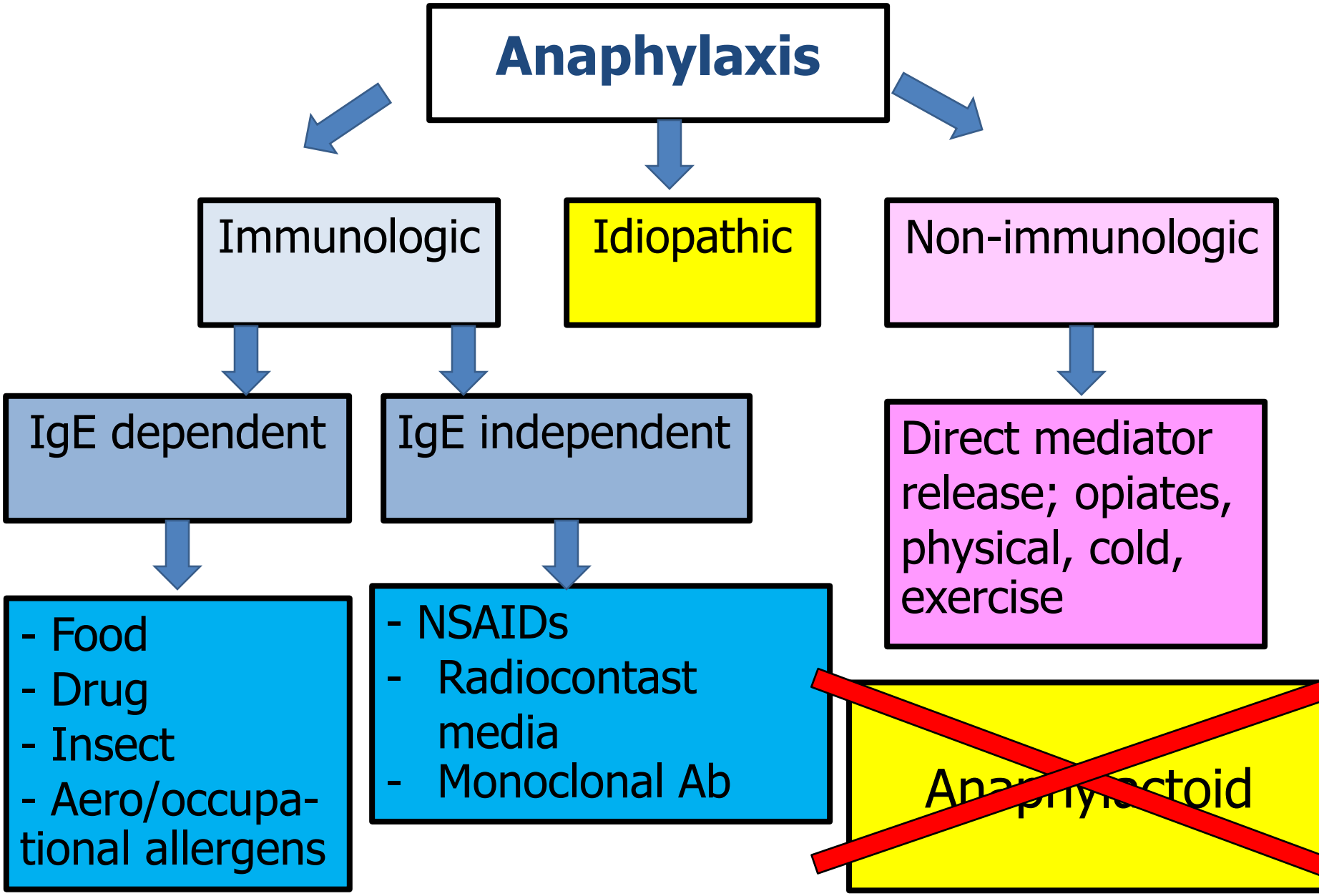
Objective

- Diagnosis
- Differential diagnosis
- Management
- Advice

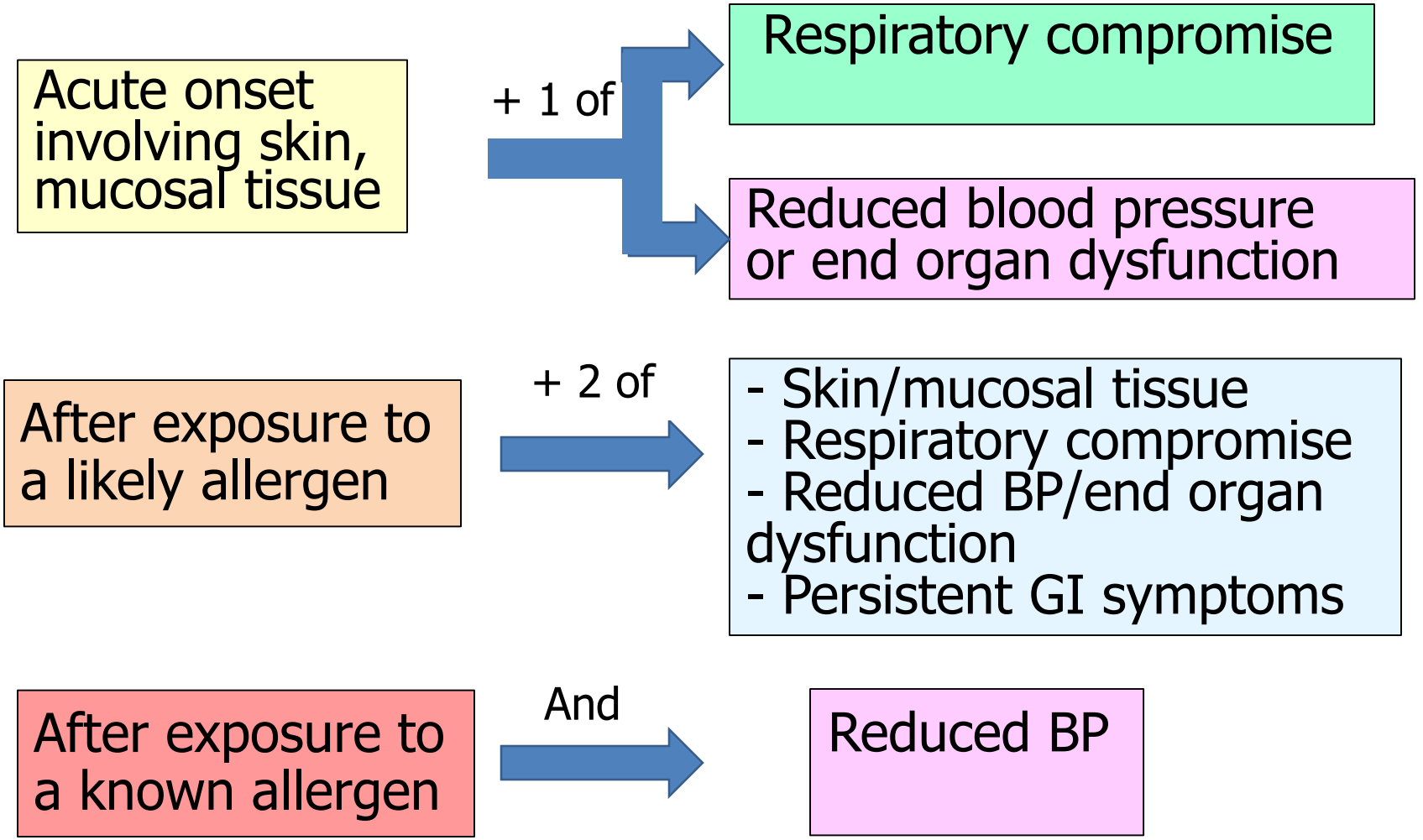
Terminology

Severe, rapid in onset, potentially life-threatening systemic hypersensitivity reaction

Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. 2014


Anaphylaxis
Immunologic
Idiopathic
Non-immunologic
IgE dependent
IgE independent
Direct mediator release; opiates, physical, cold, exercise
- Food
- Drug
- Insect
- Aero/occupa-tional allergens
- NSAIDs
- Radiocontast media
- Monoclonal Ab
Anaphylactoid

Criteria for diagnosis



Organ involvement

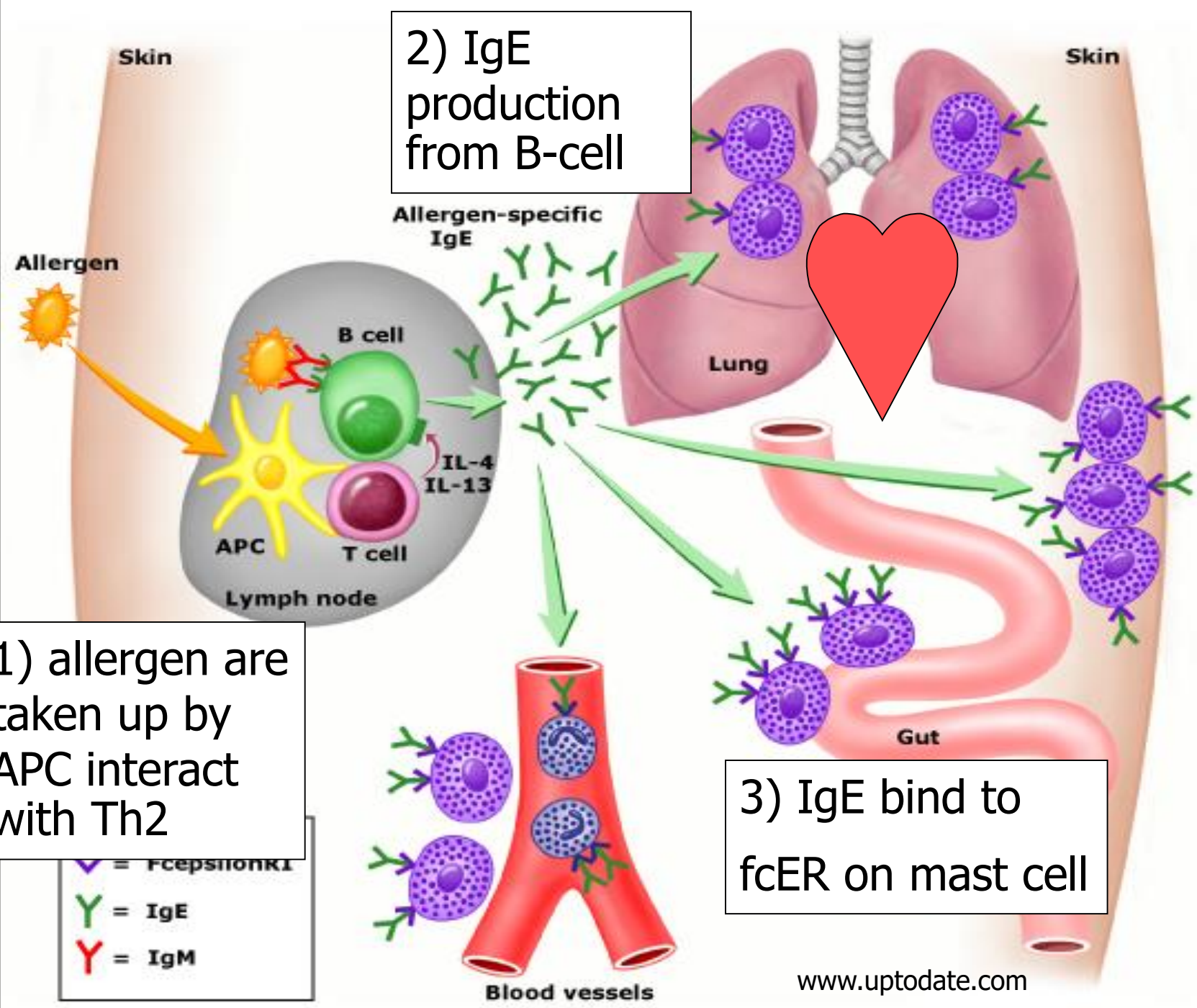
- Skin-mucosal tissue: urticaria, flush, angioedema
- Respiratory: dyspnea, wheeze, bronchospasm, stridor, hypoxemia, **cough**
- Gastrointestinal: crampy abdominal pain, vomiting, diarrhea
- Cardiovascular: reduced blood pressure, end-organ dysfunction; hypotonia, syncope, incontinence

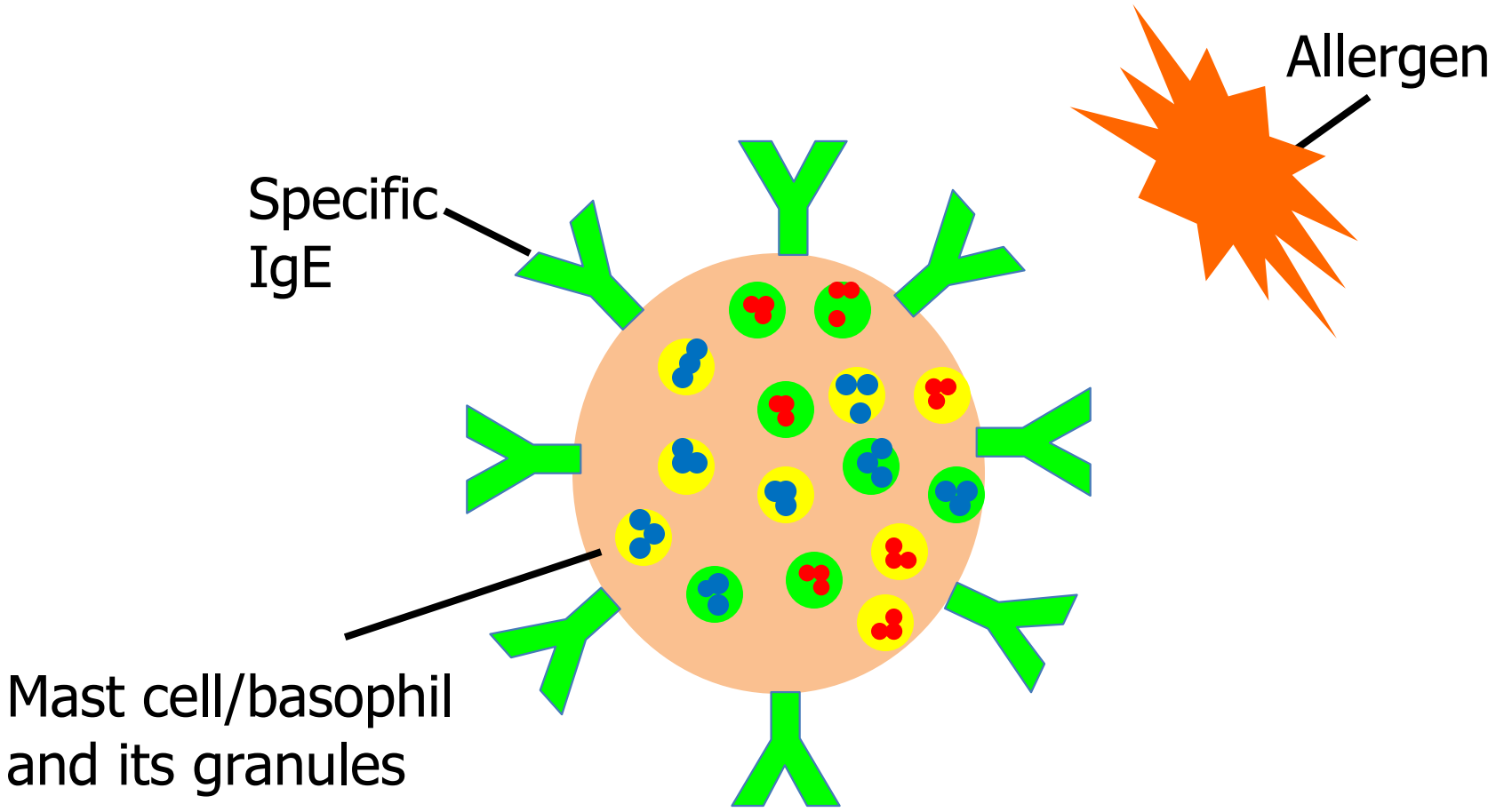
Signs and symptoms; frequency of occurrence

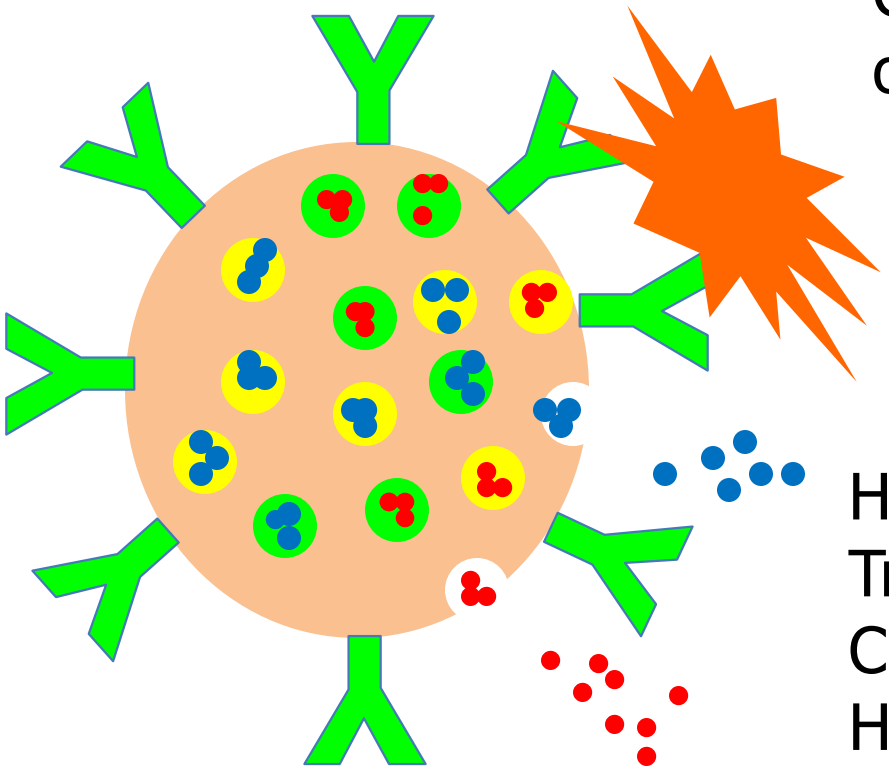
Signs/Symptoms	Percentage of Cases
Cutaneous	>90
Urticaria and angioedema	85-90
Flush	45-55
Pruritus without rash	2-5
Respiratory	40-60
Dyspnea, wheeze	45-50
Upper airway angioedema	50-60
Rhinitis	15-20
Dizziness, Syncope, Hypotension	30-35

Do not rely on hypotension or skin lesion!

J Allergy Clin Immunol 2010;126:477-80 (based on compilation of 1784 patients review)


2) IgE production from B-cell
Skin
Skin
Allergen-specific IgE
Allergen
B cell
Lung
IL-4
IL-13
APC
T cell
Lymph node
1) allergen are taken up by APC interact with Th2
Gut
3) IgE bind to fcER on mast cell
= IgE
= IgM
Blood vessels
www.uptodate.com

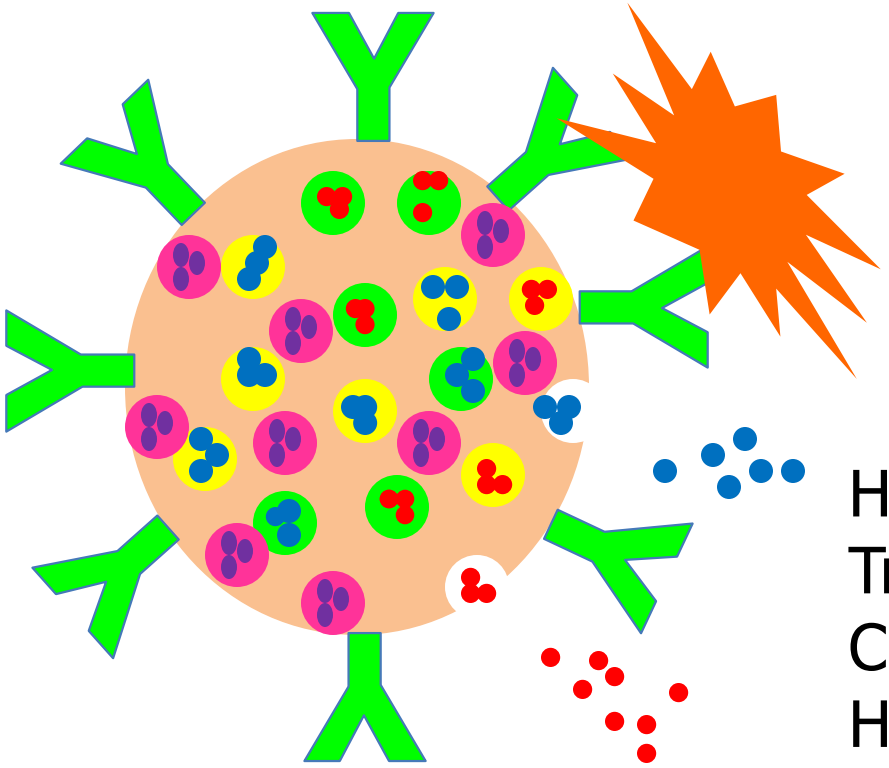

Allergen
Specific
IgE
Mast cell/basophil
and its granules



Cross-linked
of allergen

Histamine
Tryptase
Chymase
Heparin

Biphasic anaphylaxis

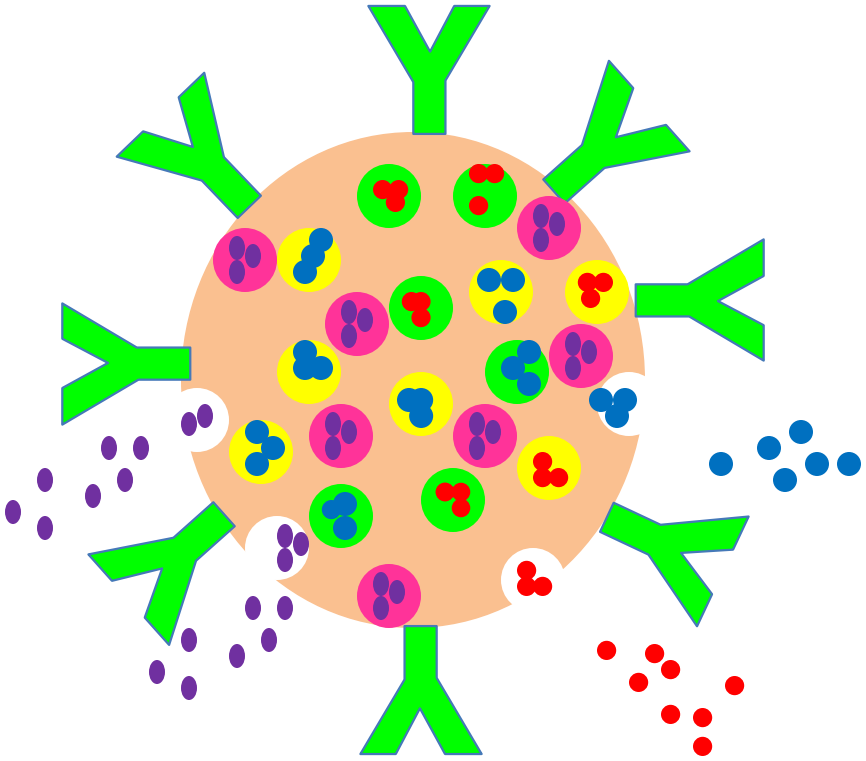


Newly generated mediators

Histamine
Tryptase
Chymase
Heparin

6-8 hours later (15-20%)

Biphasic anaphylaxis



Prostaglandin
Leukotriene
TNF-α
Chemokine

6-8 hours later (15-20%)

Mast cell and basophil mediators

Mediators	Pathophysiologic Activity	Clinical Correlates
Histamine and products of arachidonic acid metabolism (leukotrienes, thromboxane, prostaglandins, platelet-activating factor)	Smooth muscle spasm, mucus secretion, vasodilation, increased vascular permeability, activation of nociceptive neurons, platelet adherence, eosinophil activation, eosinophil chemotaxis	Wheeze, urticaria, angioedema, flush, itch, diarrhea, abdominal pain, hypotension, rhinorrhea, bronchorrhea
Neutral proteases: tryptase, chymase, carboxypeptidase, cathepsin G	Cleavage of complement components, chemoattractants for eosinophils and neutrophils, further activation and degranulation of mast cells, cleavage of neuropeptides, conversion of angiotensin I to angiotensin II	May recruit complement by cleaving C3; may ameliorate symptoms by invoking hypertensive response through angiotensin I-II conversion and by inactivating neuropeptides, although angiotensin II also may cause deleterious coronary artery vasoconstriction. Also, proteases can magnify response because of further mast cell activation.
Proteoglycans: heparin, chondroitin sulfate	Anticoagulation, inhibition of complement, phospholipase A_2 binding, chemoattractant for eosinophils, cytokine inhibition, kinin pathway activation	Can prevent intravascular coagulation and recruitment of complement. Can recruit kinins, increasing severity of reaction.
Chemoattractants: chemokines, eosinophil chemotactic factors	Summons cells to site	May be partly responsible for recrudescence of symptoms in late phase reaction or extension and protraction of reaction
Tumor necrosis factor α activates nuclear factor-κB	Produces platelet-activating factor (PAF)	Vascular permeability and vasodilation; PAF synthesized and released late, involved in late phase reactions

Summary: effect of mediators

Pathophysiology	Clinical
smooth muscle spasm	
- Bronchi	Wheeze
- Coronary arteries	Myocardial ischemia
- GI tract	Nausea, vomiting, diarrhea
Increased vascular permeability and vasodilatation	Flush, urticaria and angioedema, hypotension
Myocardial depression	Hypotension, poor perfusion
Increased grandular secretion	Bronchorrhea, rhinorhea

Differential diagnosis

Vasomotor reaction	Excessive histamine
•Flush syndromes •Medullary carcinoma thyroid •Autonomic epilepsy	•Systemic mastocytosis •Urticaria pigmentosa •Basophilic leukemia •Hydatid cyst
Restaurant syndrome	**Non organic disease**
•Monosodium glutamate •Sulfites •Scombroidosis	•Panic attacks •Munchausen stridor •Vocal cord dysfunction
Other form of shock	**Miscellaneous**
Hemorrhagic Cardiogenic Endotoxic	•Hereditary angioedema •Urticarial vasculitis •Pheochromocytoma •Hyper-IgE, urticaria syndrome •Neurologic (seizure, stroke) •Red man syndrome •Capillary leak syndrome

Common disorder	Clnical presentation	Anaphylaxis
Urticaria/angioedema	Limited to skin and subcutaneous tissues	Involvement of one or more body system
Asthma exacerbation	Isolated respiratory symptoms	Onset within minutes or a few hours after exposure to a likely trigger
Vasovagal syncope	Diaphoresis, nausea, vomiting, bradycardia, pallor	Flushing, itching, urticaria, angioedema, respiratory compromised, tachycardia
Other forms of shock	More gradual, onset	Sudden onset

Ongoing symptoms that are consistent with anaphylaxis, the patient should receive adrenaline promptly!

Laboratory findings

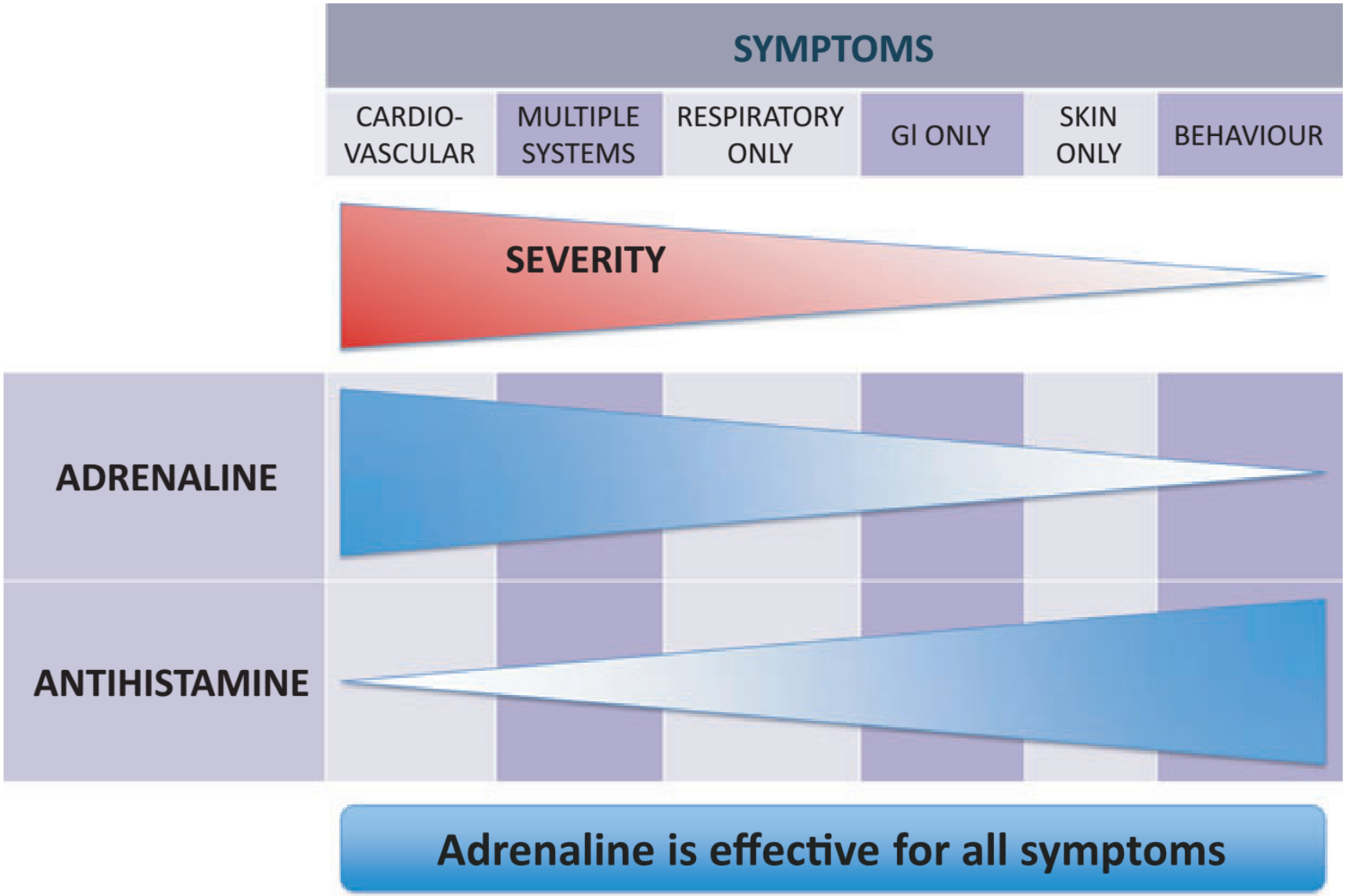
- Tryptase: 60 min-4 hours
- Plasma and urine histamine: 5-60 mins
- Platelet activating factor level: correlate with severity
- Allergologic work up; Skin test, specific IgE,

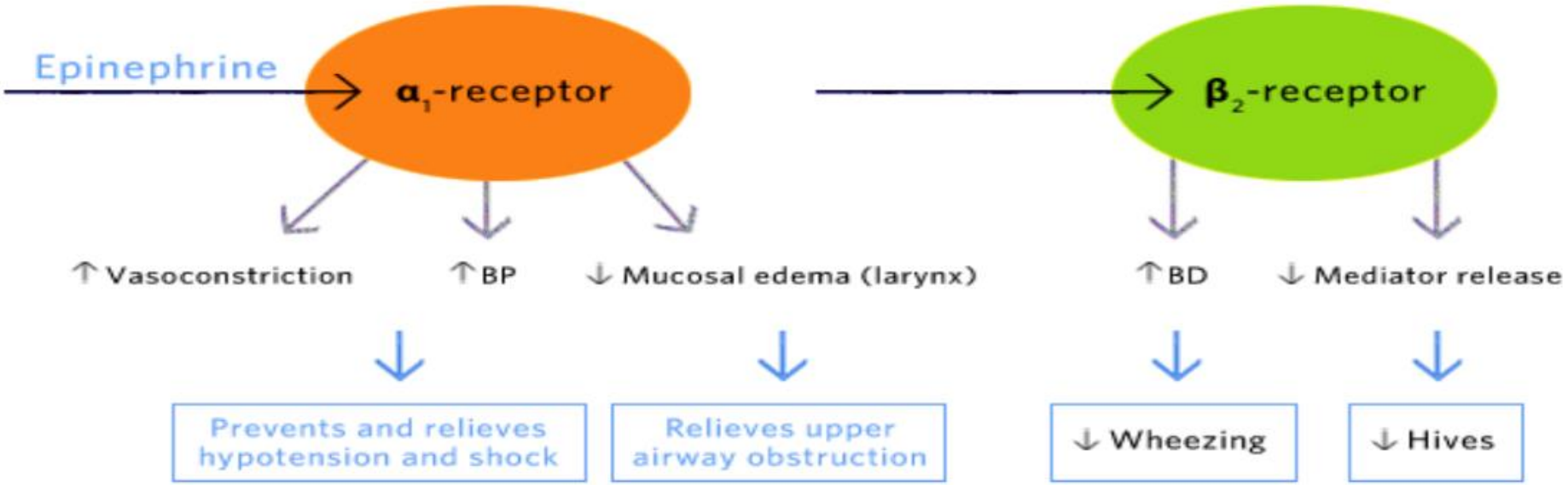
No definite biomarker.
Diagnosis rely on clinical presentation!

Emergency management

Adrenaline

- Drug of choice for anaphylaxis
- Pharmacologic actions address the pathophysiologic changes
- Decreases mediator release from mast cells
- The only medication that prevents or reverses obstruction to airflow and cardiovascular collapse

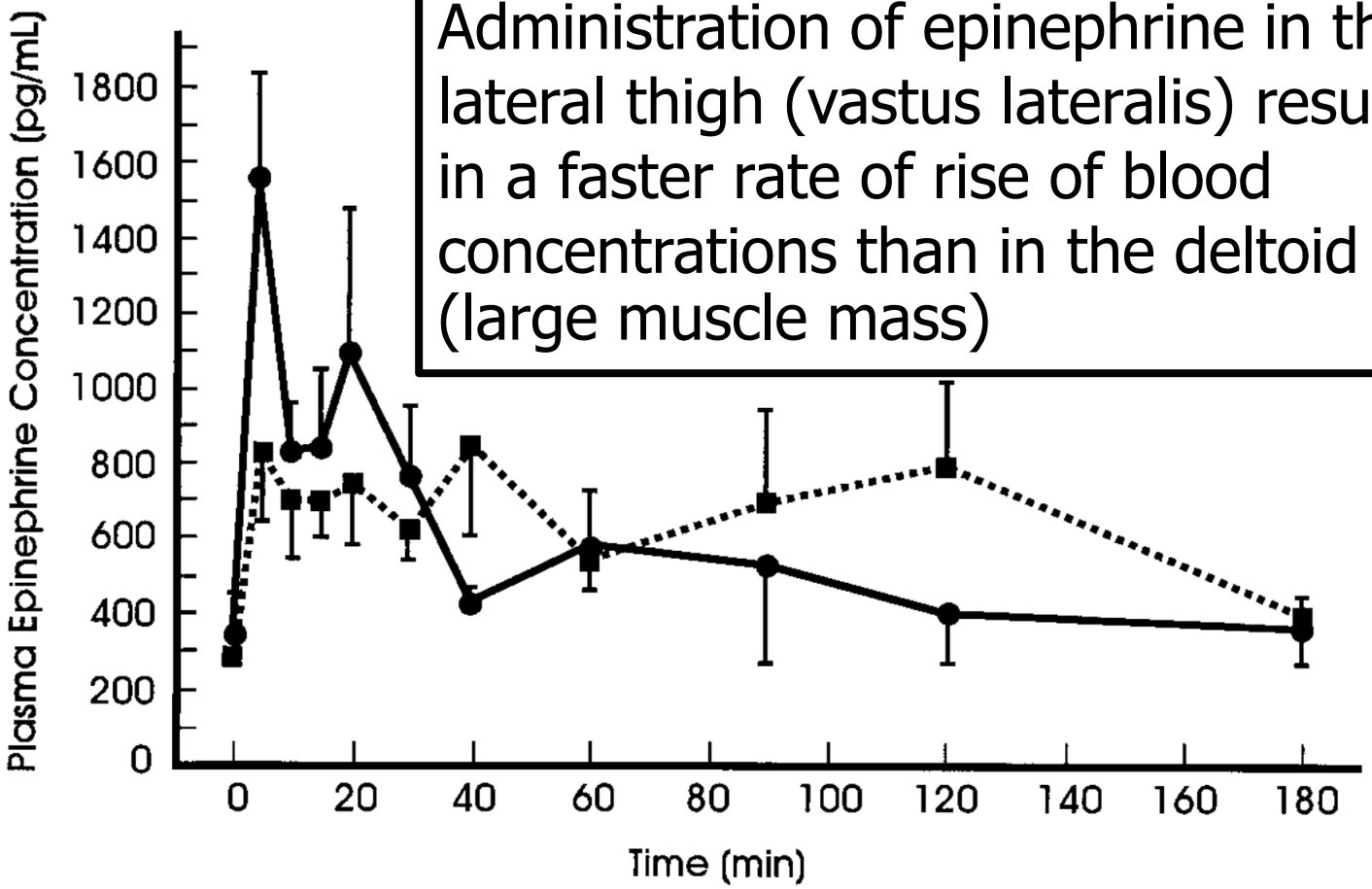

SYMPTOMS
CARDIO-VASCULAR
MULTIPLE SYSTEMS
RESPIRATORY ONLY
GI ONLY
SKIN ONLY
BEHAVIOUR
SEVERITY
ADRENALINE
ANTIHISTAMINE
Adrenaline is effective for all symptoms



Additional pharmacologic effects: at β_1-receptor: ↑ heart rate; ↑ cardiac contraction force

BP = blood pressure; BD=bronchodilation

Adrenaline absorption : intramuscular VS subcutaneous



Administration of epinephrine in the lateral thigh (vastus lateralis) results in a faster rate of rise of blood concentrations than in the deltoid (large muscle mass)

J Allergy Clin Immunol 1998;101:33-7

Intravenous adrenaline

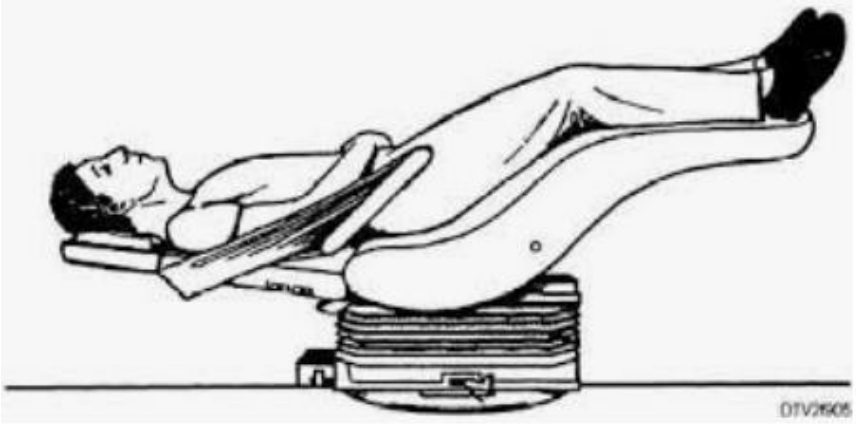
- severe hypotension, cardiovascular collapse, no response to repeated IM administration (poor absorption)
- Continuous infusion is superior to IV bolus
- IV bolus injections in cardiac arrest
- IV adrenaline in patients with adequate circulation may cause life-threatening hypertension, myocardial ischemia, arrhythmias
- should be monitored with continuous ECG, pulse oximetry, and frequent noninvasive blood pressures

Intravenous fluid

- Massive fluid shifts due to increased vascular permeability combined with the effects of vasodilation
- Initiated in orthostasis, hypotension
- Normal saline 10-20 mL per kilogram in 5-10 minutes

Positioning

- Respiratory distress → sitting up
- Circulatory instability → lying on back with the lower extremities elevated
- Unconscious → recovery position
- Avoid sudden abrupt change to a more upright posture



Oxygen

- High-flow oxygen should be administered by face mask
- Patients with hypotension or tachypnea
- Improve acidosis→ improve adrenaline absorption

Adjunctive treatment

H1 antihistamines

- Relieving itching and hives
- Do not relieve airway obstruction, gastrointestinal symptoms, shock
- Do not inhibit mediator release from mast cells

H2 antihistamines

- May provide some additional benefit of vasodilatation; decreased headache (one study in mild reaction)

Not drug of choice!

Ann Emerg Med 2000;36: 462-8

Adjunctive treatment

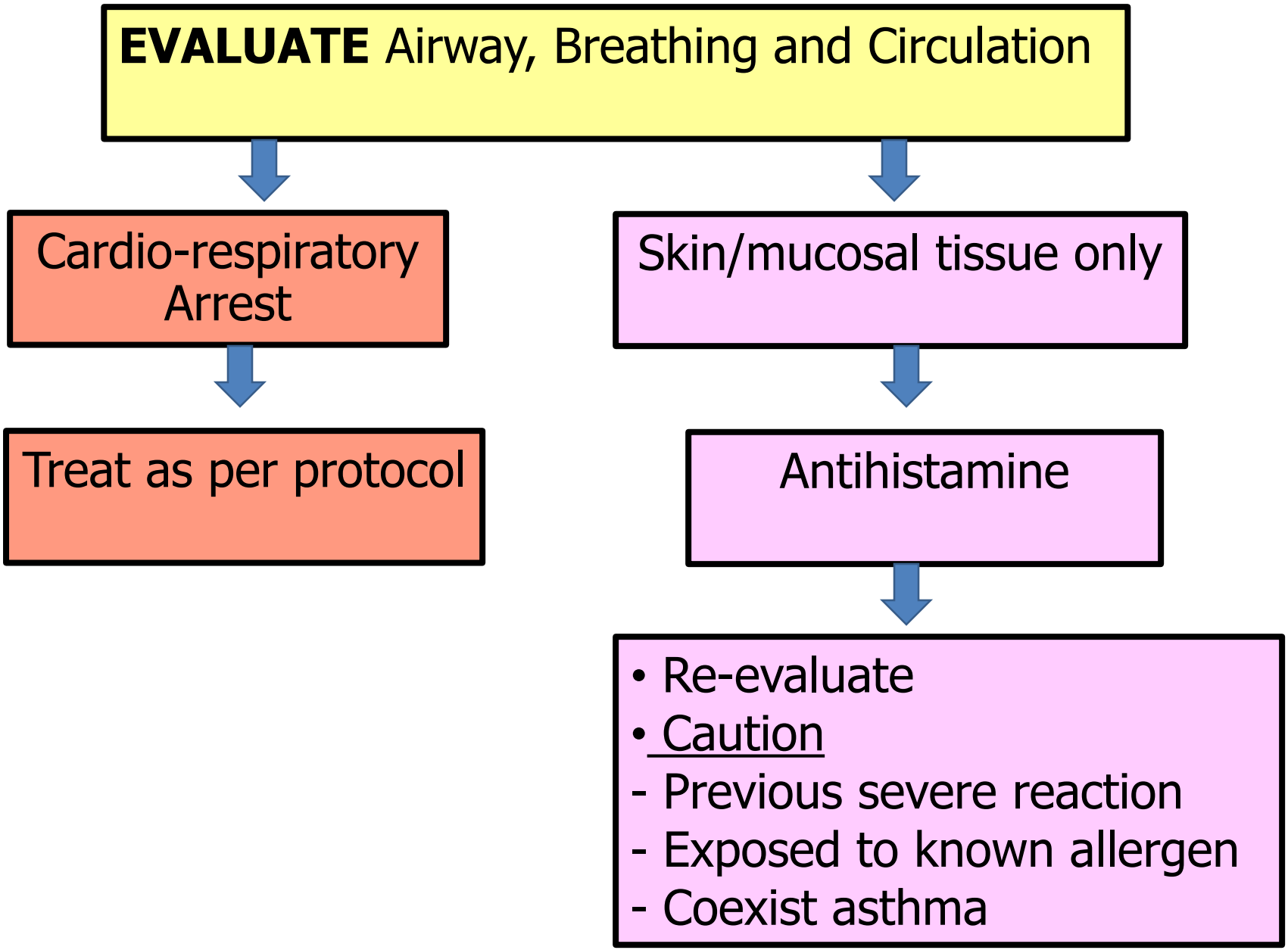
Inhaled β-adrenergic agonists

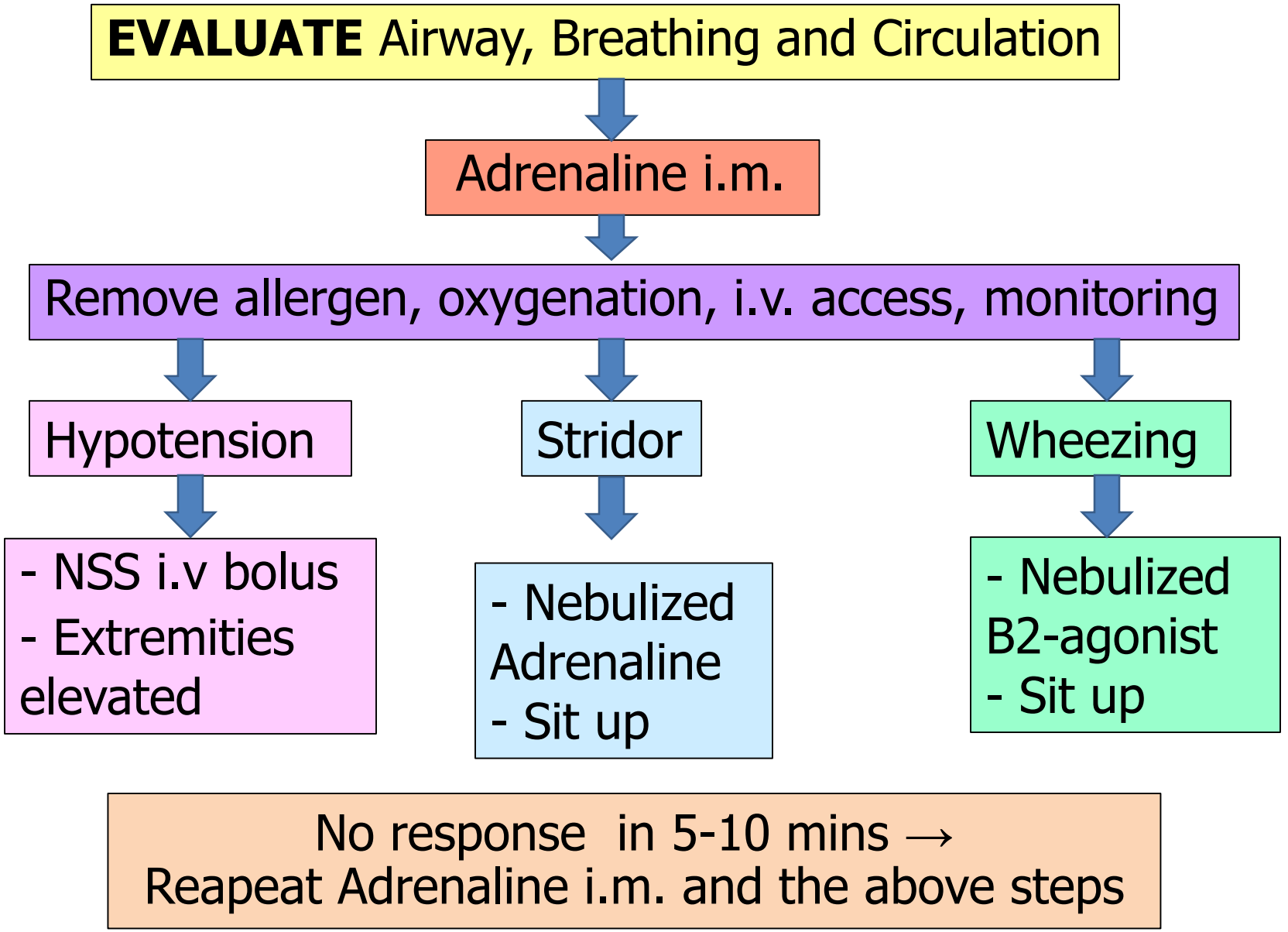
- Treatment of bronchospasm not responsive to adrenaline
- Do not prevent or relieve mucosal edema in the upper airway

Glucocorticoids

- Onset of action takes 4-6 hours
- Do not relieve the initial symptoms
- ? Prevent protracted and biphasic anaphylaxis (no clear evidence)
- Stopped after three days without a taper

Ann Allergy Asthma Immunol 2005;95: 217-28


EVALUATE Airway, Breathing and Circulation
Cardio-respiratory Arrest
Skin/mucosal tissue only
Treat as per protocol
Antihistamine
• Re-evaluate
• Caution
- Previous severe reaction
- Exposed to known allergen
- Coexist asthma



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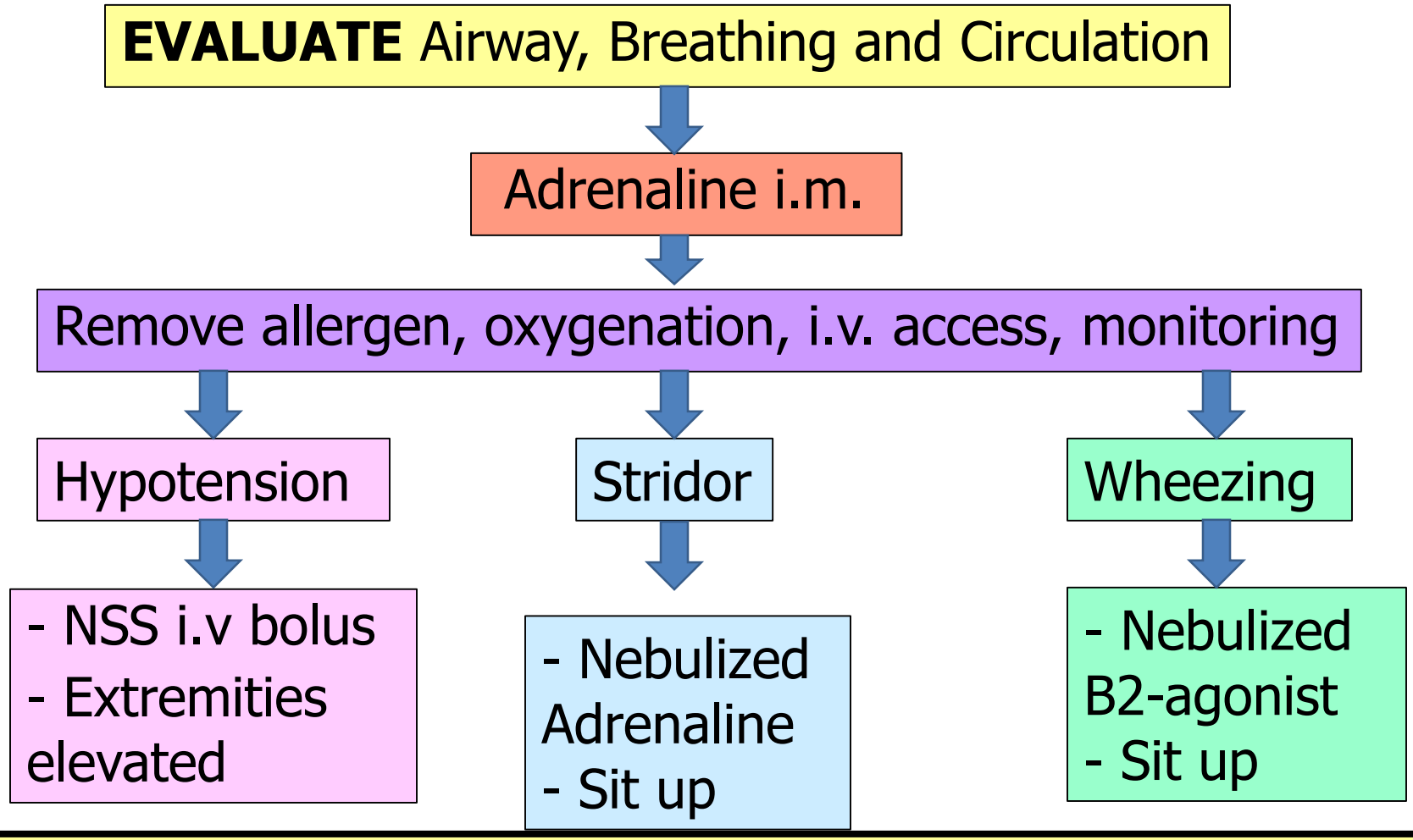
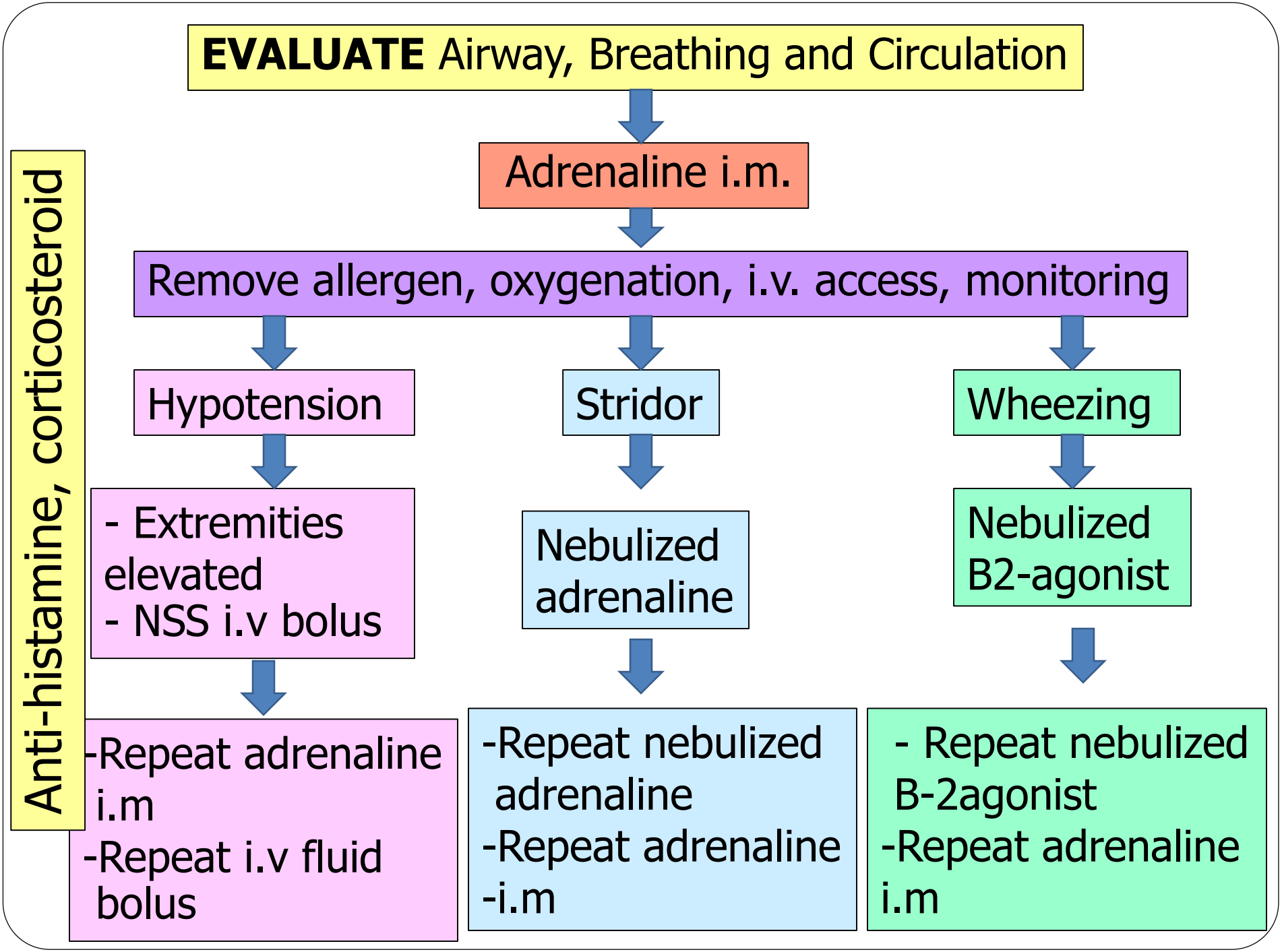


Adrenaline i.v (infusion)

:profoundly hypotensive ,failed to respond to i.v.fluid **and** several (2-3)doses of adrenaline i.m


EVALUATE Airway, Breathing and Circulation
Adrenaline i.m.
Remove allergen, oxygenation, i.v. access, monitoring
Anti-histamine, corticosteroid
Hypotension
- Extremities elevated
- NSS i.v bolus
-Repeat adrenaline i.m
-Repeat i.v fluid bolus
Stridor
Nebulized adrenaline
-Repeat nebulized adrenaline
-Repeat adrenaline -i.m
Wheezing
Nebulized B2-agonist
- Repeat nebulized B-2agonist
-Repeat adrenaline i.m

Dosage and route of administration

Drug	Dose/Route	Comment
Adrenaline (1:1,000)	0.01 mg/kg/dose (max 0.3mg) i.m. lateral thigh	- Initial drug of choice - repeat every 5-15 minutes
ANTIHISTAMINES		
Diphenhydramine	1-2 mg/kg/dose (max 50 mg)	Second line treatment
Chlopheniramine	0.25 mg/kg i.v	Dose for anaphylaxis
Ranitidine	1 mg/kg i.v (max 50 mg)	

Drug	Dose/Route	Comment
CORTICOSTEROIDS		
Hydrocortisone	4-8 mg /kg i.v (max 100 mg)	Exact dose not established Adapted from asthma treatment
Methylprednisolone	1-2 mg/kg/dose i.v (max 50 mg)	
Prednisolone	1-2 mg/kg/day p.o. (max 40 mg)	For mild episode
DRUGS FOR BRONCHOSPASM		
Aerosolized β-agonist (salbutalmol)	Solution : 0.03 mg/kg/dose (max 5 mg) Nebule: (2.5 mg/2.5ml) 1-2 nebules	- Dose = asthma - Bronchospasm not responding to adrenaline

Common pitfalls

- Reluctant to diagnose anaphylaxis in the absence of shock/skin lesions
- Anaphylaxis in a known asthmatic may be mistaken for an asthma exacerbation
- Patients may not recognize the symptoms as a serious allergic reaction
- Reluctant to use adrenaline → fatality

Observation period

- No consensus or RCT, at least 4-8hours
- Biphasic episodes
- Longer observation period (8 to 24 hours) esp in
  - Severe/ protracted anaphylaxis; hypotension or collapse
  - Underlying asthma, cardiovascular, using B-blocker
  - Ingested antigen with possibility of continued absorption
  - Previous history of biphasic response

Discharge planning

Prednisolone

- 1-2 mkd/day for 72 hours

Counseling

- They have anaphylaxis which is a life-threatening condition
- Symptoms may recur up to three days
- Risk for repeat episodes

Allergen identification and avoidance

- Avoidance
- Immunotherapy
- Desensitization
- Premedication

Discharge planning

Acute managent

- Rapid recognition of symptoms
- Administer adrenaline
- Emergency medical service

Adrenaline for emergencies

- Provide the patient with a self-injectable adrenaline
- Importance of carrying the adrenaline at all times
- Educate family members

Epipen autoinjector

- EpiPen® (adrenaline) 0.3 mg
- EpiPen Jr® (adrenaline) 0.15 mg

Adrenaline kit


Adrenali
0.5
1.5
2
2.5
3m

When to refer

- Allergen identification
- Recurrent
- Severe reaction
- Immunotherapy; insect

Take home message

Either shock or skin/mucosal lesion are not required for the diagnosis

Adrenaline is the first line drug