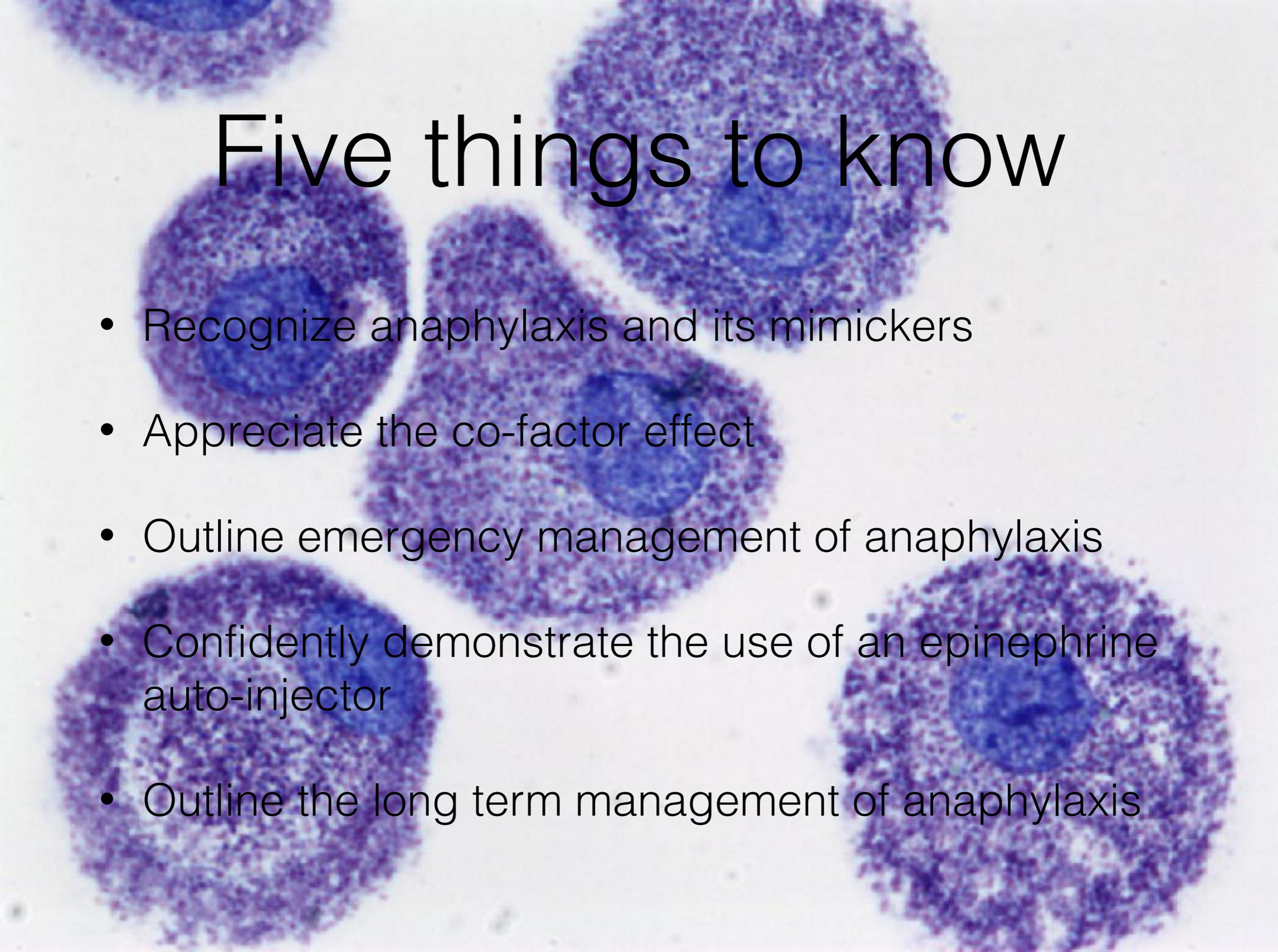


Five things to know about anaphylaxis

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New Brunswick Internal Medicine Update
April 22, 2016

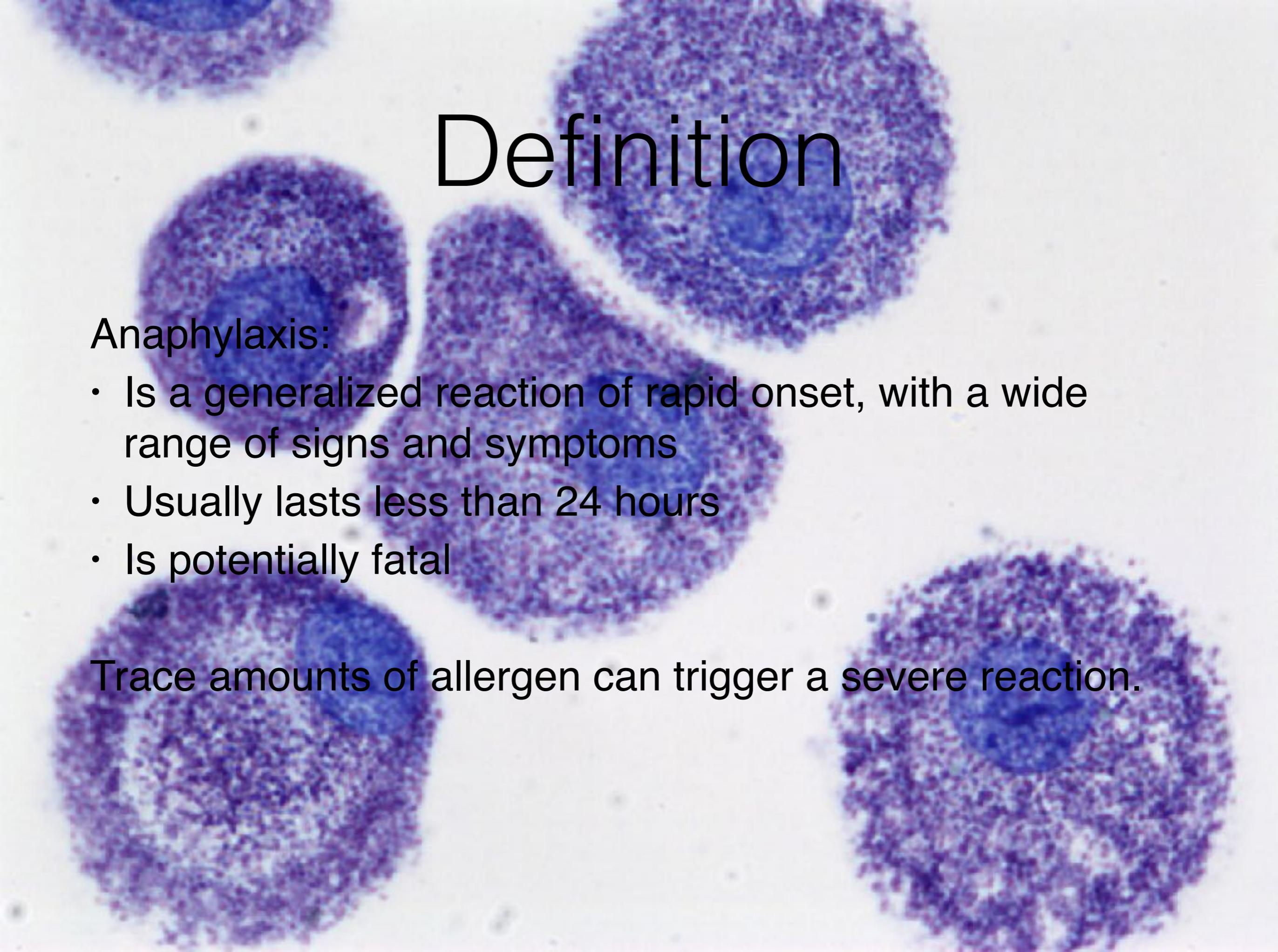
Disclosures

- None relevant to this presentation



Five things to know

- Recognize anaphylaxis and its mimickers
- Appreciate the co-factor effect
- Outline emergency management of anaphylaxis
- Confidently demonstrate the use of an epinephrine auto-injector
- Outline the long term management of anaphylaxis



Definition

Anaphylaxis:

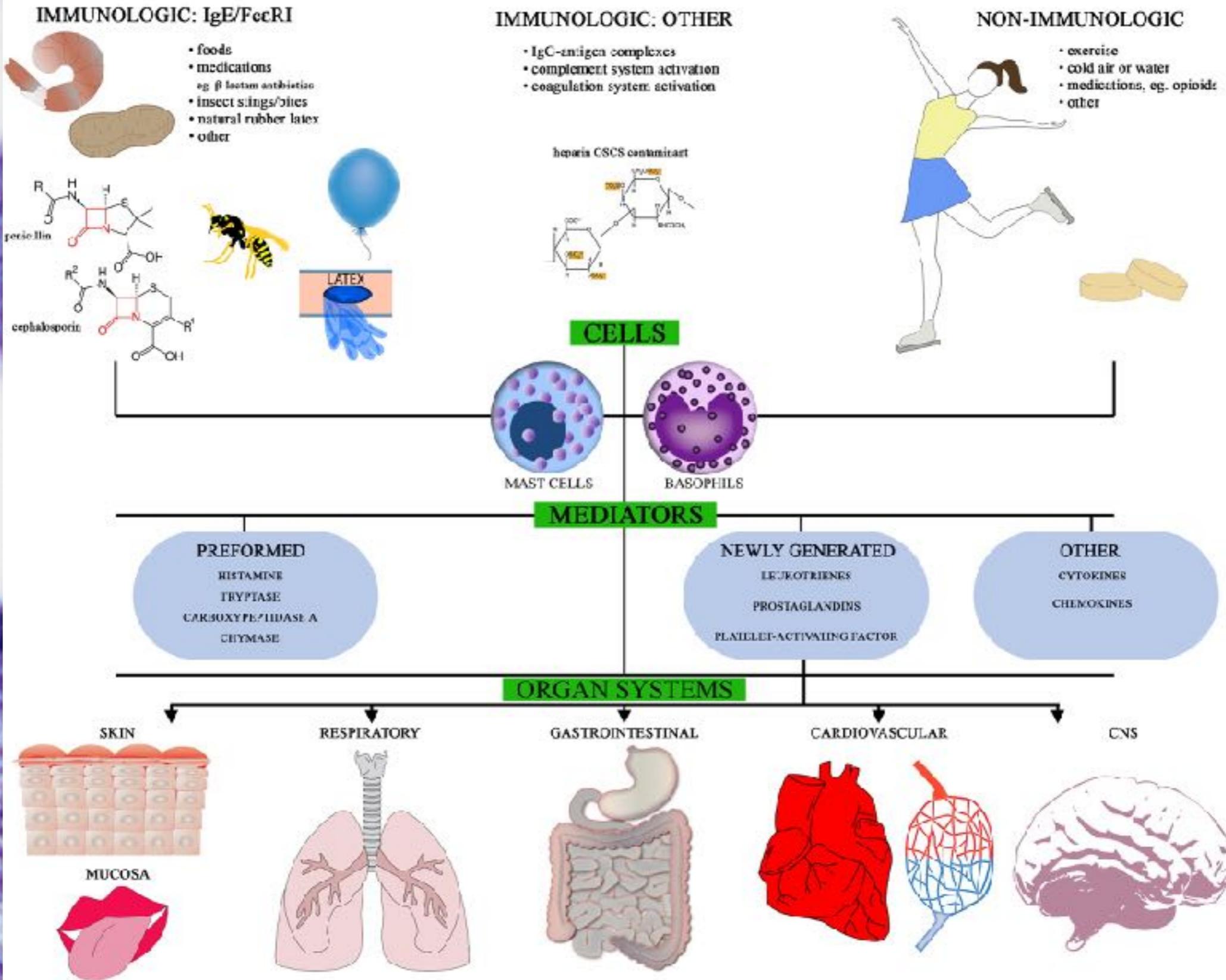
- Is a generalized reaction of rapid onset, with a wide range of signs and symptoms
- Usually lasts less than 24 hours
- Is potentially fatal

Trace amounts of allergen can trigger a severe reaction.

Triggers of anaphylaxis

- IgE-mediated anaphylaxis:
 - Foods, insect venoms, medications (NSAIDs, beta lactams, biologic agents) latex, radiocontrast media
- Non-IgE mediated anaphylaxis:
 - Radiocontrast media, medications (NSAIDs, biologic agents)
- Direct mast cell activation
 - Physical factors (exercise, cold, heat, sun), ethanol, medications (opioids)
- Idiopathic anaphylaxis

MECHANISMS AND TRIGGERS



Mediator Effects

- **Histamine:** vasodilation, increased vascular permeability, heart rate, cardiac contraction, glandular secretion
- **Prostaglandin D₂:** bronchoconstriction, pulmonary and coronary vasoconstriction, peripheral vasodilation
- **Leukotrienes:** bronchoconstriction, increased vascular permeability
- **PAF:** bronchoconstriction, increased vascular permeability
- **TNF- α :** activation of neutrophils, recruitment of other effector cells, enhanced chemokine synthesis

PAF = platelet activating factor
TNF- α = tumor necrosis factor- α

Prevalence

- True prevalence of anaphylaxis is unknown but estimated at 2% (from food + insect stings)
- Based on epinephrine prescriptions:
 - 0.95% in the general population
 - >1.44% in children under 17 years of age
 - 314,440 – 476,625 Canadians affected

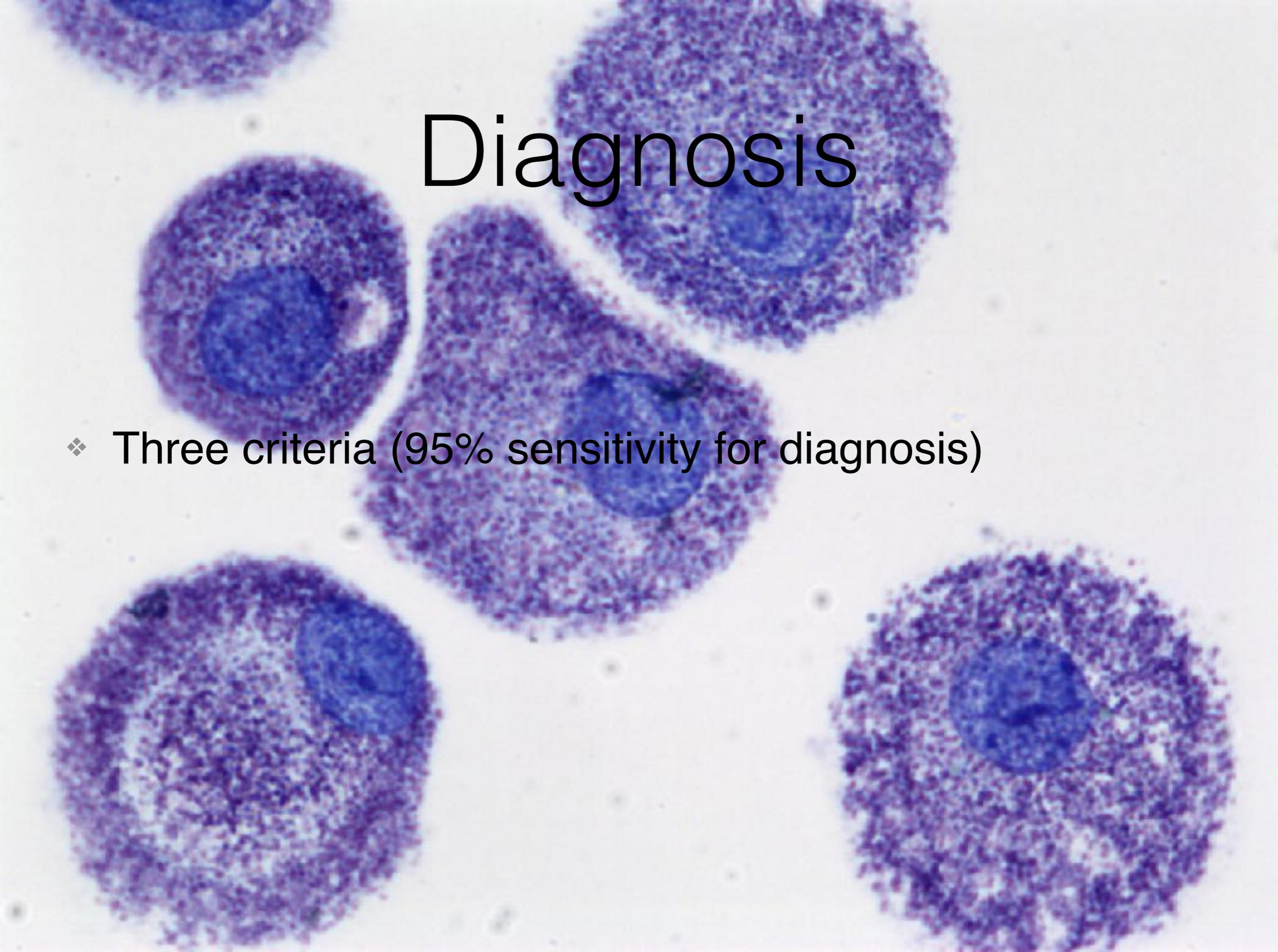
Epinephrine dispensing patterns for an out-of-hospital population: (Simons FE et al JACI 2002)

Mechanisms

IMMUNOLOGIC MECHANISMS (IgE dependent)					
<p>peanut tree nuts shellfish fish</p>		<p>stinging insects</p>		<p>β-lactam antibiotics* NSAIDs* ** biologic agents*</p>	
<p>milk egg soybean peach sesame</p>					
Foods		Venoms		Medications*	
<p>Natural rubber latex Occupational allergens</p>		<p>Seminal fluid Aeroallergens</p>		<p>Radiocontrast media*</p>	
IMMUNOLOGIC MECHANISMS (IgE independent)					
<p>Radiocontrast media*</p>		<p>NSAIDs* **</p>		<p>Dextrans (e.g. HMW*** iron or other source)</p>	
				<p>Biologic agents* (e.g. some monoclonal antibodies)</p>	
NONIMMUNOLOGIC MECHANISMS (Direct mast cell activation)					
<p>Physical factors (e.g. exercise, cold, heat, sunlight)</p>			<p>Ethanol</p>		<p>Medications* (e.g. opioids)</p>
IDIOPATHIC ANAPHYLAXIS (No apparent trigger)					
<p>Previously unrecognized allergen?</p>			<p>Mastocytosis/clonal mast cell disorder?</p>		
<p>*Trigger anaphylaxis by more than one mechanism **NSAIDs, non-steroidal anti-inflammatory drugs ***HMW, high molecular weight</p>					

Simons, F. E. R. *et al.* World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organ. J.* 4, 13–37 (2011).

Diagnosis



- ❖ Three criteria (95% sensitivity for diagnosis)

Anaphylaxis is highly likely when

**Sudden onset of an illness (minutes to several hours),
with involvement of the skin, mucosal tissue, or both
(e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)**

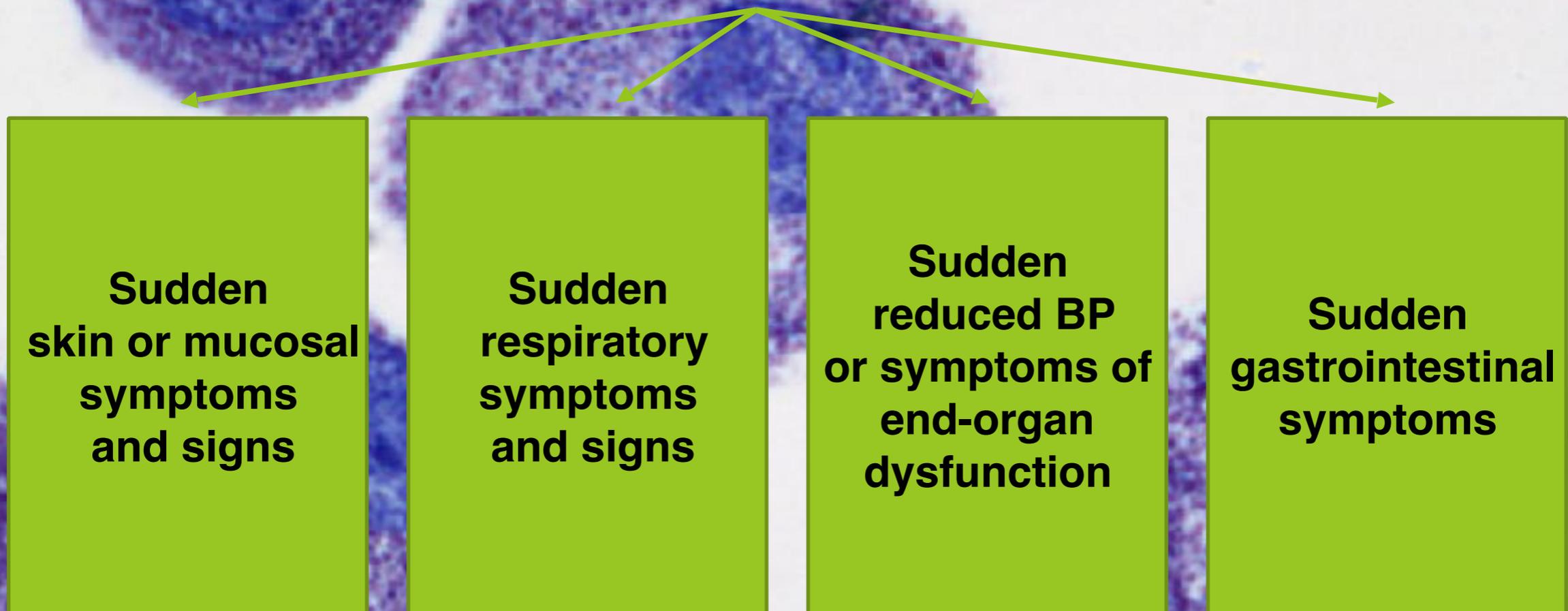
AND AT LEAST ONE OF THE FOLLOWING :

**Sudden
respiratory
symptoms
and signs**

**Sudden reduced BP
or symptoms
of end-organ
dysfunction**

Anaphylaxis is highly likely when

Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger for that patient (minutes to several hours):



Anaphylaxis is highly likely when

**Reduced blood pressure (BP)
after exposure to a known allergen for that patient
(minutes to several hours)**

INFANTS AND CHILDREN:

**Low systolic BP
(age-specific)
or greater than
30% decrease
in systolic BP**

ADULTS:

**Systolic BP of
less than 90 mm Hg
or greater than
30% decrease
from that person's baseline**

Signs and symptoms

TABLE E1. Frequency of occurrence of signs and symptoms of anaphylaxis*†‡

Signs and Symptoms	Percent
Cutaneous	
Urticaria and angioedema	85-90
Flushing	45-55
Pruritus without rash	2-5
Respiratory	
Dyspnea, wheeze	45-50
Upper airway angioedema	50-60
Rhinitis	15-20
Dizziness, syncope, hypotension	30-35
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25-30
Miscellaneous	
Headache	5-8
Substernal pain	4-6
Seizure	1-2

*On the basis of a compilation of 1865 patients reported in references.^{1 through 14}

†Percentages are approximations.

‡Children may have a lower frequency of cutaneous symptoms in anaphylaxis.

Differential diagnosis

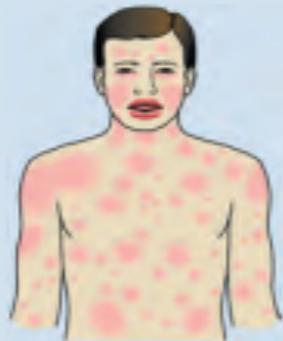
TABLE 4. Differential Diagnosis of Anaphylaxis

Common diagnostic dilemmas	Flush syndromes
Acute asthma ^a	Peri-menopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Autonomic epilepsy
Acute generalized urticaria ^a	Medullary carcinoma of the thyroid
Aspiration of a foreign body	
Cardiovascular (myocardial infarction ^a , pulmonary embolus)	Nonorganic Disease
Neurologic events (seizure, cerebrovascular event)	Vocal cord dysfunction
	Hyperventilation
	Psychosomatic episode
Postprandial syndromes	
Scombroidosis ^b	Shock
Pollen-food allergy syndrome ^c	Hypovolemic
Monosodium glutamate	Cardiogenic
Sulfites	Distributive ^d
Food poisoning	Septic
Excess endogenous histamine	Other
Mastocytosis/clonal mast cell disorders ^e	Nonallergic angioedema
Basophilic leukemia	Hereditary angioedema types I, II, & III
	ACE inhibitor-associated angioedema
	Systemic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

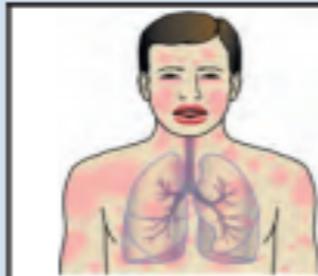
1. Recognize anaphylaxis and its mimickers

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

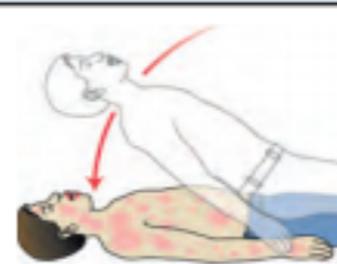
1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)



And at least one of the following:



Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)

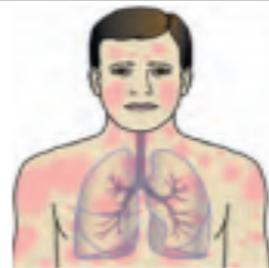


Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

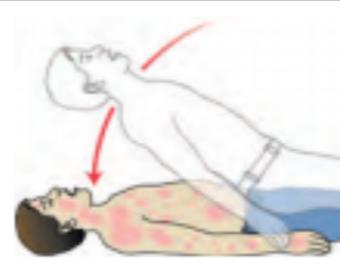
Or **2** Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours):



Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)



Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)



Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)



Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

Or **3** Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours):



Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***



Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

* For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation)

** For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.

*** Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year less than (70mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years. Normal heart rate ranges from 80-140 beats/minutes at age 1-2 years; from 80-120 beats/minute at age 3 years; and from 70-115 beats/minute after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.

Differential Diagnosis

Angioedema/urticaria

Asthma

Syncope

Panic attack

Acute cardiac or neurologic events

Postprandial syndromes

Scombroid, MSG, sulfites, food poisoning

Excess endogenous histamine

mastocytosis/clonal mast cell disorder

Flushing syndromes

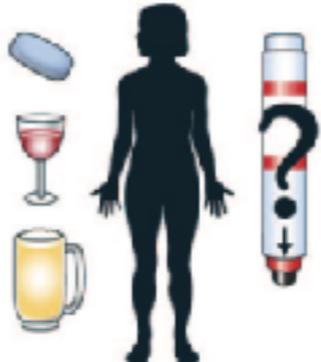
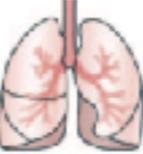
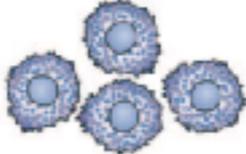
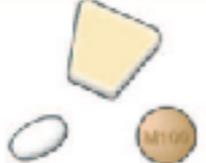
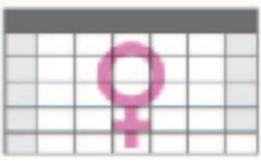
Non-organic disease

Simons, F. E. R. *et al.* 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr. Opin. Allergy Clin. Immunol.* 12, 389-399 (2012).

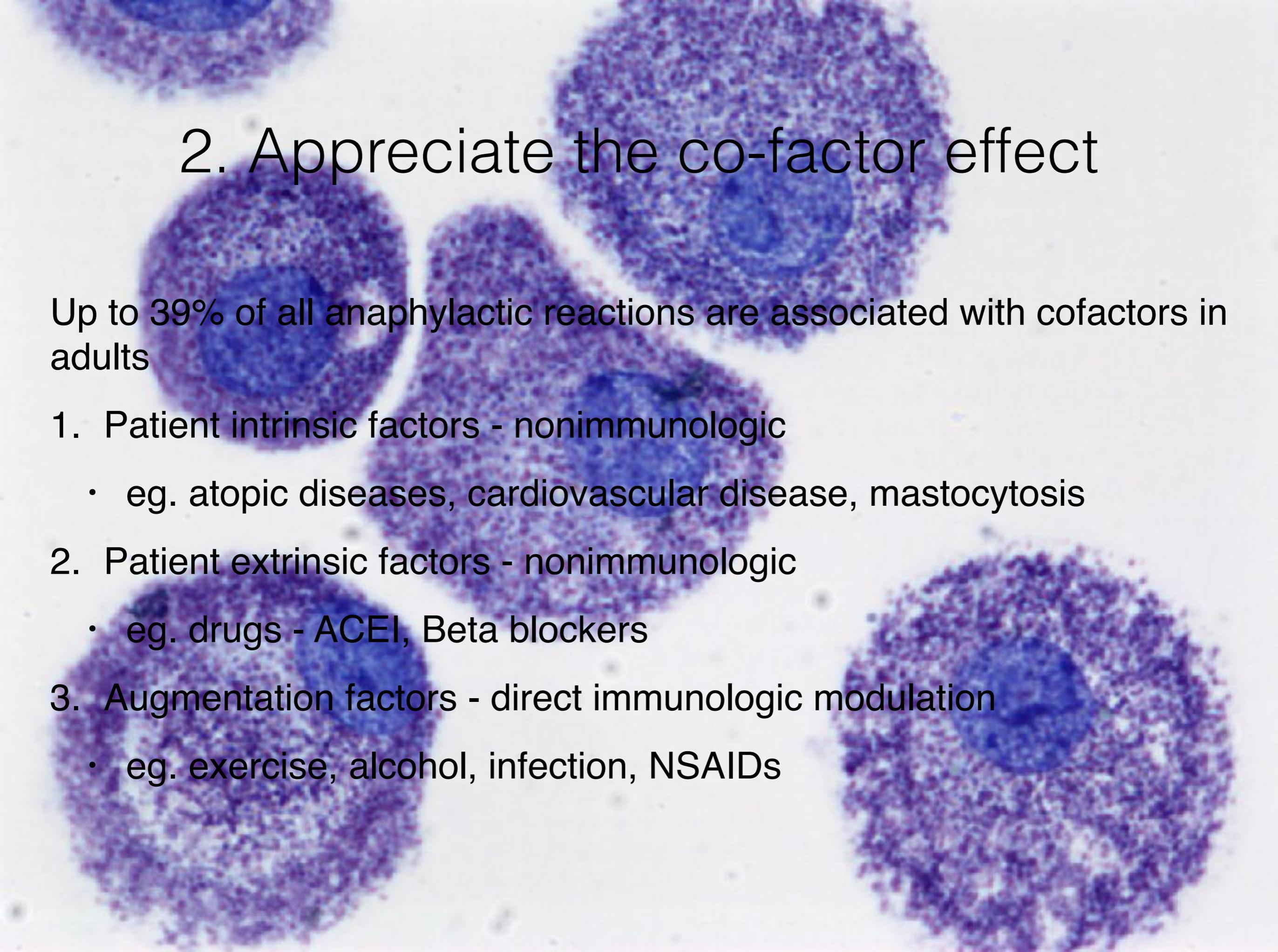
Patient co-factors

- Patient co-factors: age-related factors, concomitant disease, and concurrent medications, which may
 - Amplify anaphylaxis
 - Impair recognition of anaphylaxis
 - Reduce epinephrine's effect
 - Sensitize patients to epinephrine's effect
- Up to 39% of cases of anaphylaxis may involve co-factors

Patient co-factors

AGE-RELATED FACTORS*				
				
Infants Cannot describe their symptoms	Adolescents and young adults Increased risk-taking behaviors	Labor and delivery Risk from medications (e.g. antibiotic to prevent neonatal group B strep infection)	Elderly Increased risk of fatality from medication or venom-triggered anaphylaxis	
CONCOMITANT DISEASES*				
				
Asthma and other respiratory diseases	Cardiovascular diseases	Mastocytosis/clonal mast cell disorders	Allergic rhinitis and eczema**	Psychiatric illness (e.g. depression)
CONCURRENT MEDICATIONS/ETHANOL/RECREATIONAL DRUG USE*				
				
β-adrenergic blockers and ACE inhibitors***		Ethanol/sedatives/hypnotics/antidepressants/recreational drugs (potentially affect recognition of anaphylaxis triggers and symptoms)		
CO-FACTORS THAT AMPLIFY ANAPHYLAXIS*				
				
Exercise	Acute infection (e.g. a cold or fever)	Emotional stress	Disruption of routine (e.g. travel)	Premenstrual status (females)
* Age-related factors, concomitant diseases, and concurrent medications potentially contribute to severe or fatal anaphylaxis. Co-factors potentially amplify anaphylaxis. Multiple factors and co-factors likely contribute to some anaphylactic episodes.				
** Atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex, but not for anaphylaxis triggered by insect stings.				
*** ACE, angiotensin-converting enzyme				

Simons, F. E. R. *et al.* World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organ. J.* 4, 13-37 (2011).



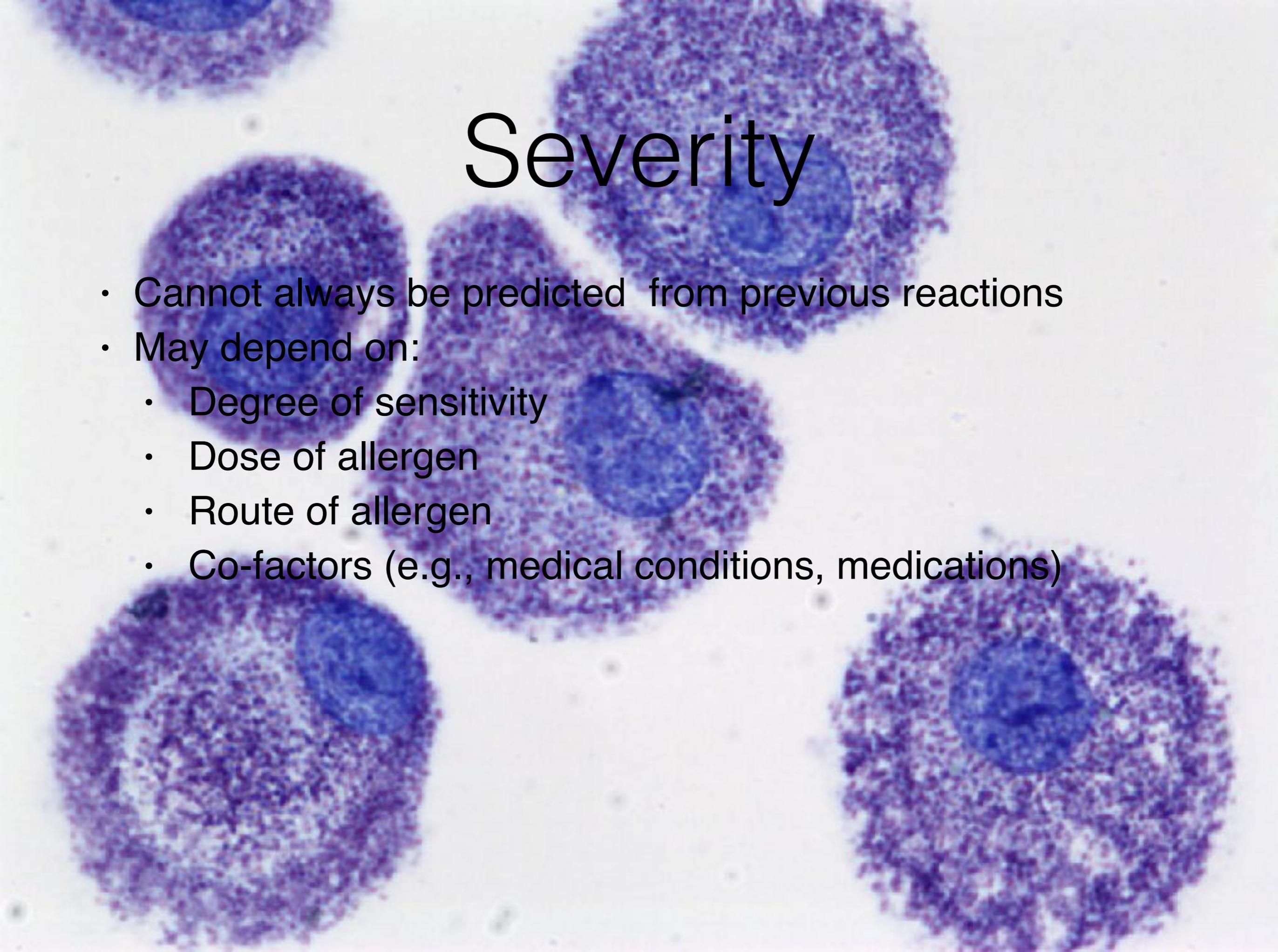
2. Appreciate the co-factor effect

Up to 39% of all anaphylactic reactions are associated with cofactors in adults

1. Patient intrinsic factors - nonimmunologic
 - eg. atopic diseases, cardiovascular disease, mastocytosis
2. Patient extrinsic factors - nonimmunologic
 - eg. drugs - ACEI, Beta blockers
3. Augmentation factors - direct immunologic modulation
 - eg. exercise, alcohol, infection, NSAIDs

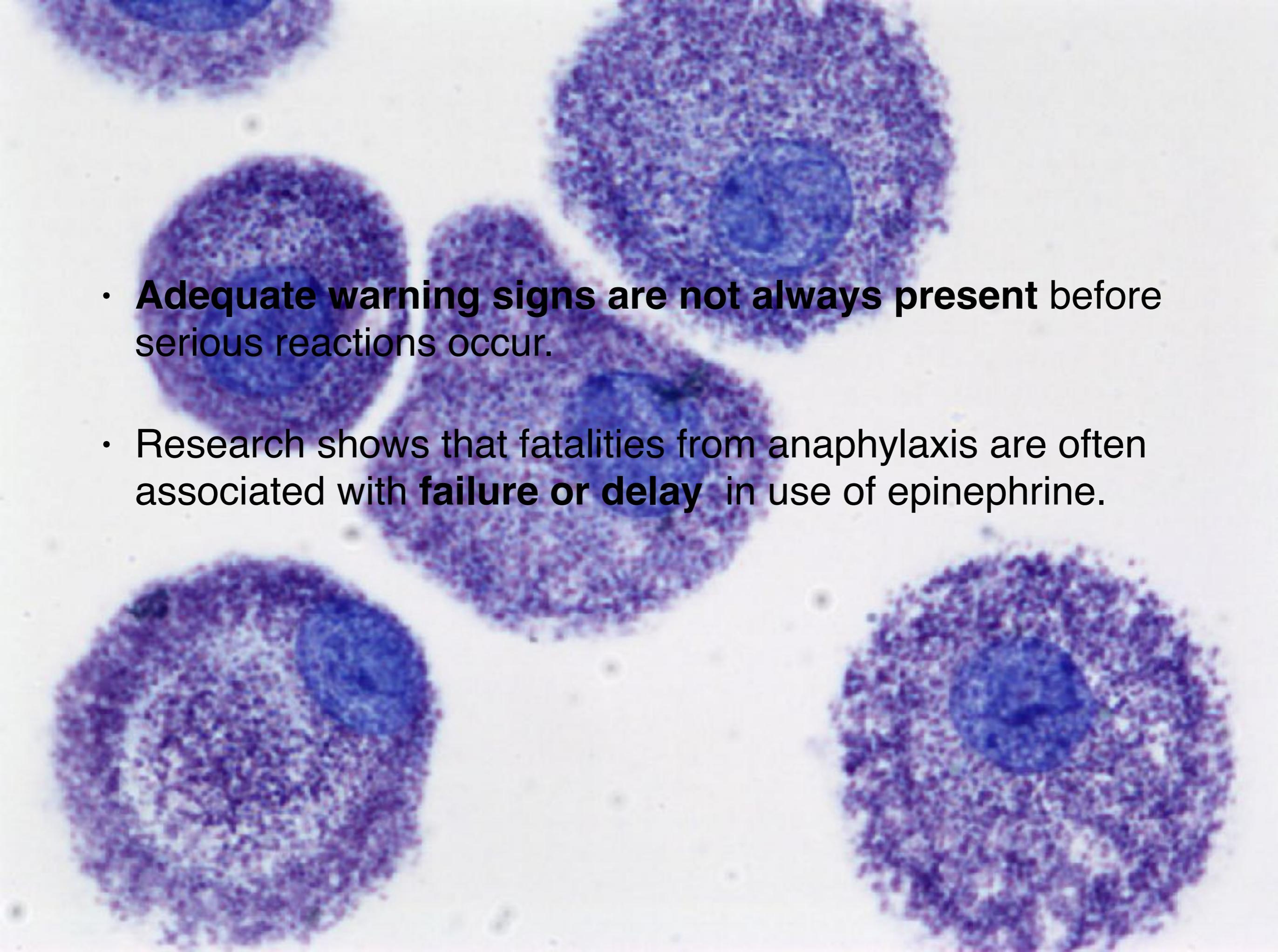
Course & Severity

- Typically **uniphasic**
- Up to ~**20%** will be **biphasic**
- Patients should stay in close proximity to a hospital or where they can call 911 for the next **48 hours** after treatment for anaphylaxis
- **Protracted anaphylaxis** (rare) has poor prognosis



Severity

- Cannot always be predicted from previous reactions
- May depend on:
 - Degree of sensitivity
 - Dose of allergen
 - Route of allergen
 - Co-factors (e.g., medical conditions, medications)

- 
- **Adequate warning signs are not always present** before serious reactions occur.
 - Research shows that fatalities from anaphylaxis are often associated with **failure or delay** in use of epinephrine.

Recognizing anaphylaxis

- Patients at risk of anaphylaxis with previous severe reactions may be educated to administer epinephrine immediately after likely **exposure to a known allergen, even before symptoms begin**
- Teach patients to **recognize symptoms**
- Sudden onset of illness (e.g., respiratory, urticaria, flushing or swelling, dizziness or lightheadedness, abdominal pain, vomiting, etc)

3. Outline emergency management of anaphylaxis

- Epinephrine dose is either 0.3mg or 0.15mg 1:1000 (if patient is ≥ 30 kg get 0.3mg dose)
- Intramuscular injection to anterolateral thigh
- NO contraindications to using epinephrine during suspected anaphylaxis (if in doubt, use it!)
- Call 911 if epinephrine administered. Lie down if in shock.
- In ED: ABC's
 - oxygen
 - fluid resuscitation
 - adjunctive therapies (antihistamines, corticosteroids, bronchodilators, glucagon)

Epinephrine

- Epinephrine is the first-line treatment for anaphylaxis
- Epinephrine is an α and β adrenergic receptor agonist
 - α increases PVR, increasing BP and coronary artery perfusion, and reverses peripheral vasodilatation
 - β -1 has inotropic and chronotropic effects so increases HR and strength of contraction

1. Sheikh A et al. The Cochrane Library 2012, Issue 8
2. Muñoz-Furlong & Weiss. Current Allergy and Asthma Reports 2009;9:57-63
3. Simone FER. J Allergy Clin Immunol 2010;125:S161-81.
4. Wasserman et al. Allergy 2010, 65:1082-92.

Epinephrine

- Fatality rates are highest in patients in whom treatment with epinephrine is delayed
- There are no absolute contraindications to epinephrine administration in the setting of anaphylaxis
- Second dose of epinephrine may be required
- *Antihistamines must **not** be used as first-line treatment for anaphylactic reactions*

After epinephrine

- Epinephrine is emergency supportive therapy only
- Patients must be immediately transported to hospital, ideally by ambulance
- Observation in an emergency facility is recommended
- New epinephrine auto-injector prescription should be provided

Other medications

Medication	Treatment
Oxygen and fluid resuscitation	<ul style="list-style-type: none">• High-flow oxygen should be administered to patients experiencing respiratory symptoms, hypoxia or hemodynamically unstable ²• Rapid fluid resuscitation should be given to restore intravascular volume ^{1,2}
H ₁ – and H ₂ antihistamines	<ul style="list-style-type: none">• Not recommended for acute management¹• Consider second line for symptomatic treatment of urticaria-angioedema and pruritus²
Corticosteroids	<ul style="list-style-type: none">• Not recommended for acute management ²• Adjunctive medication, may help in an acute attack in preventing or shortening protracted reactions and in the treatment of recurrent idiopathic anaphylaxis ¹• Early corticosteroids treatment is beneficial in asthma ¹• Steroids do not prevent biphasic reactions ^{1,2}
Bronchodilators	<ul style="list-style-type: none">• Adjunctive medication for bronchospasms refractory to epinephrine ^{1,2}
Glucagon	<ul style="list-style-type: none">• In patients taking β-blockers - If administration of epinephrine is ineffective, glucagon can be used. Airway protection must be ensured because glucagon causes emesis²

4. Confidently demonstrate the use of an epinephrine auto-injector

- Currently only EpiPen is available on the market (no Twinject or Allerject)



1
Blue to the sky.

- Hold firmly with orange tip pointing downward.
- **Remove blue safety cap by pulling straight up. Do not bend or twist.**



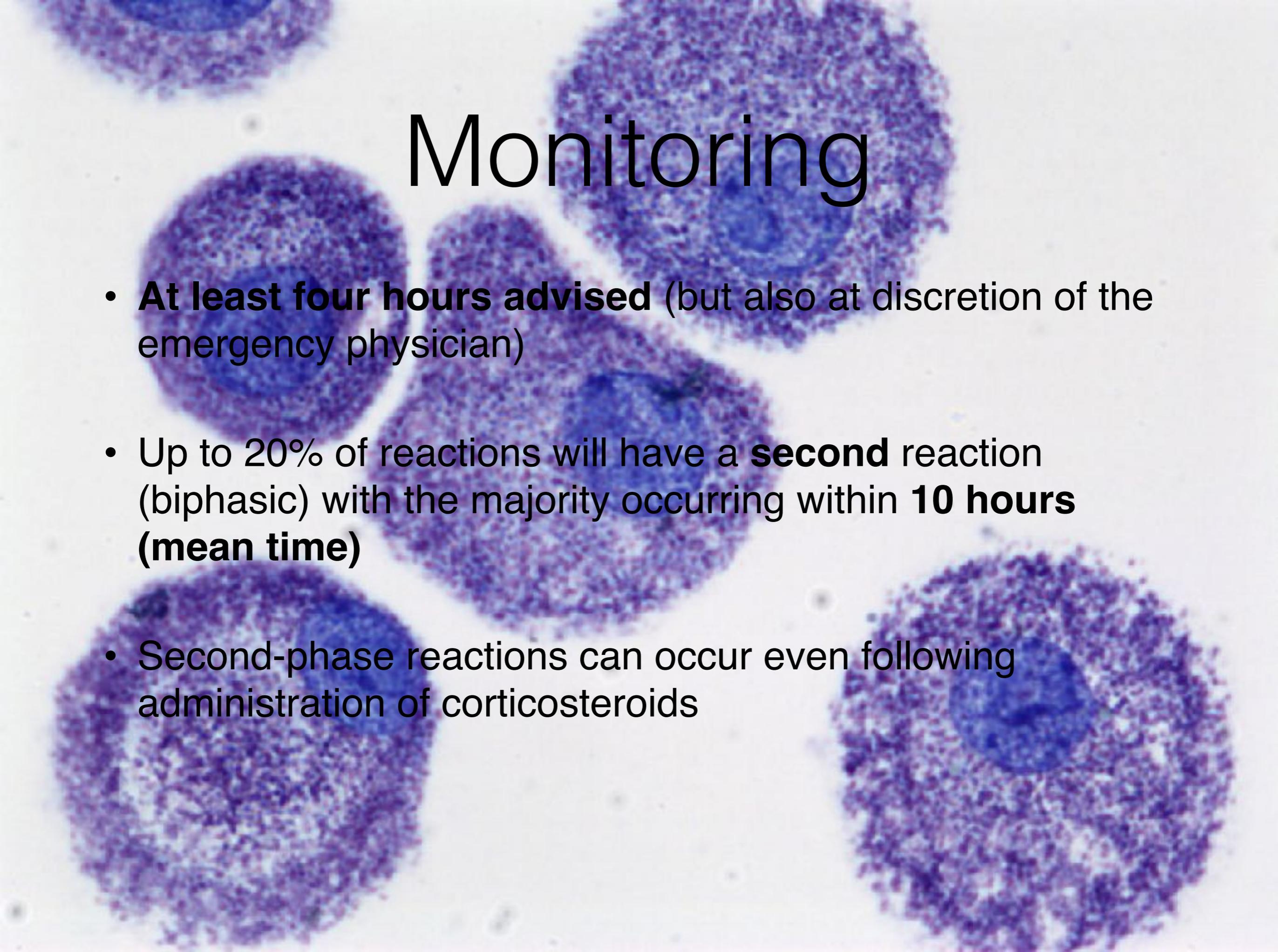
2
Orange to the thigh.

- **Swing and push orange tip firmly into mid-outer thigh until you hear a 'click'.**
- Hold on thigh for several seconds.



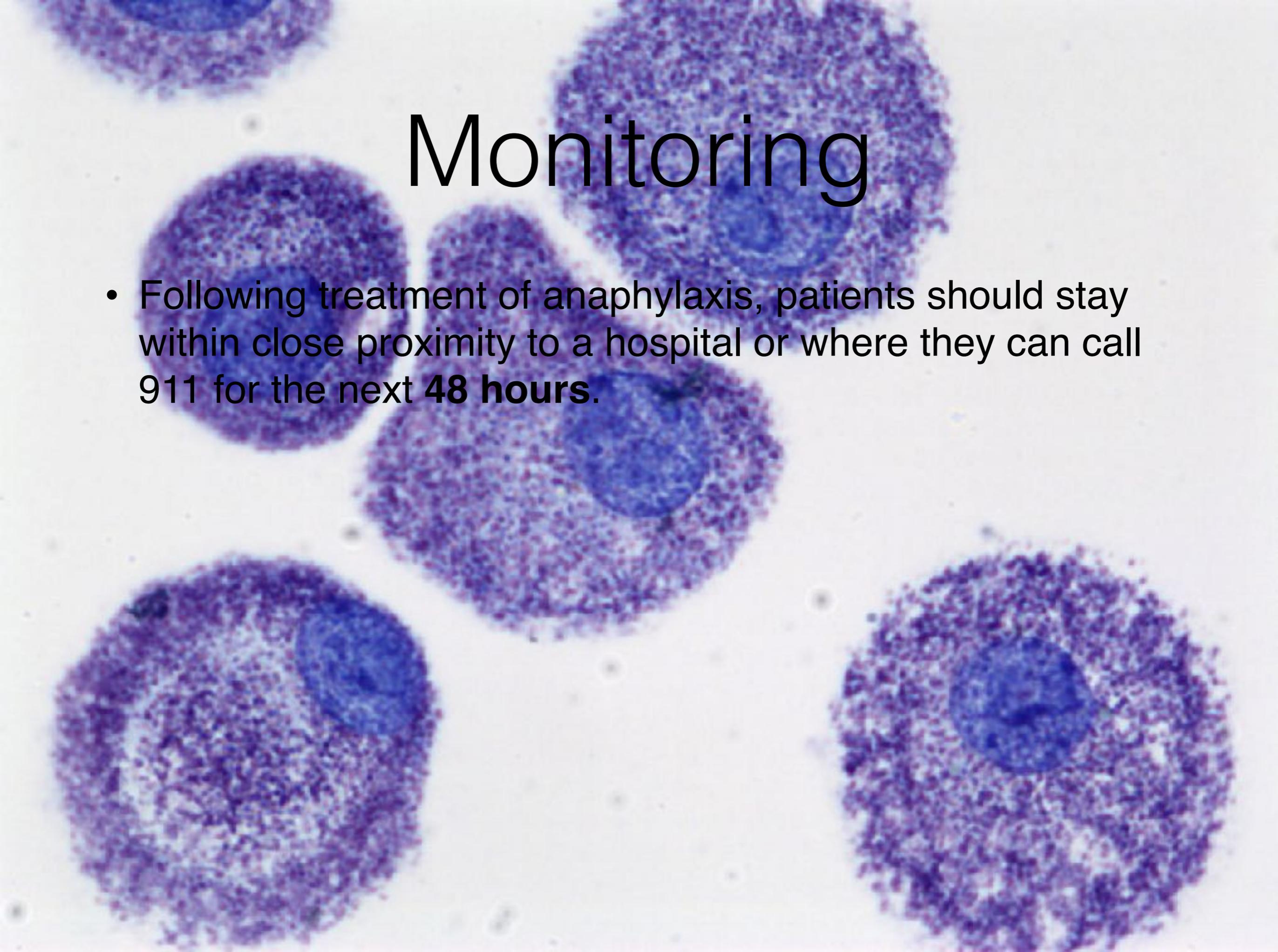
Built-in needle protection

- After injection, the orange cover automatically extends to ensure the needle is never exposed.



Monitoring

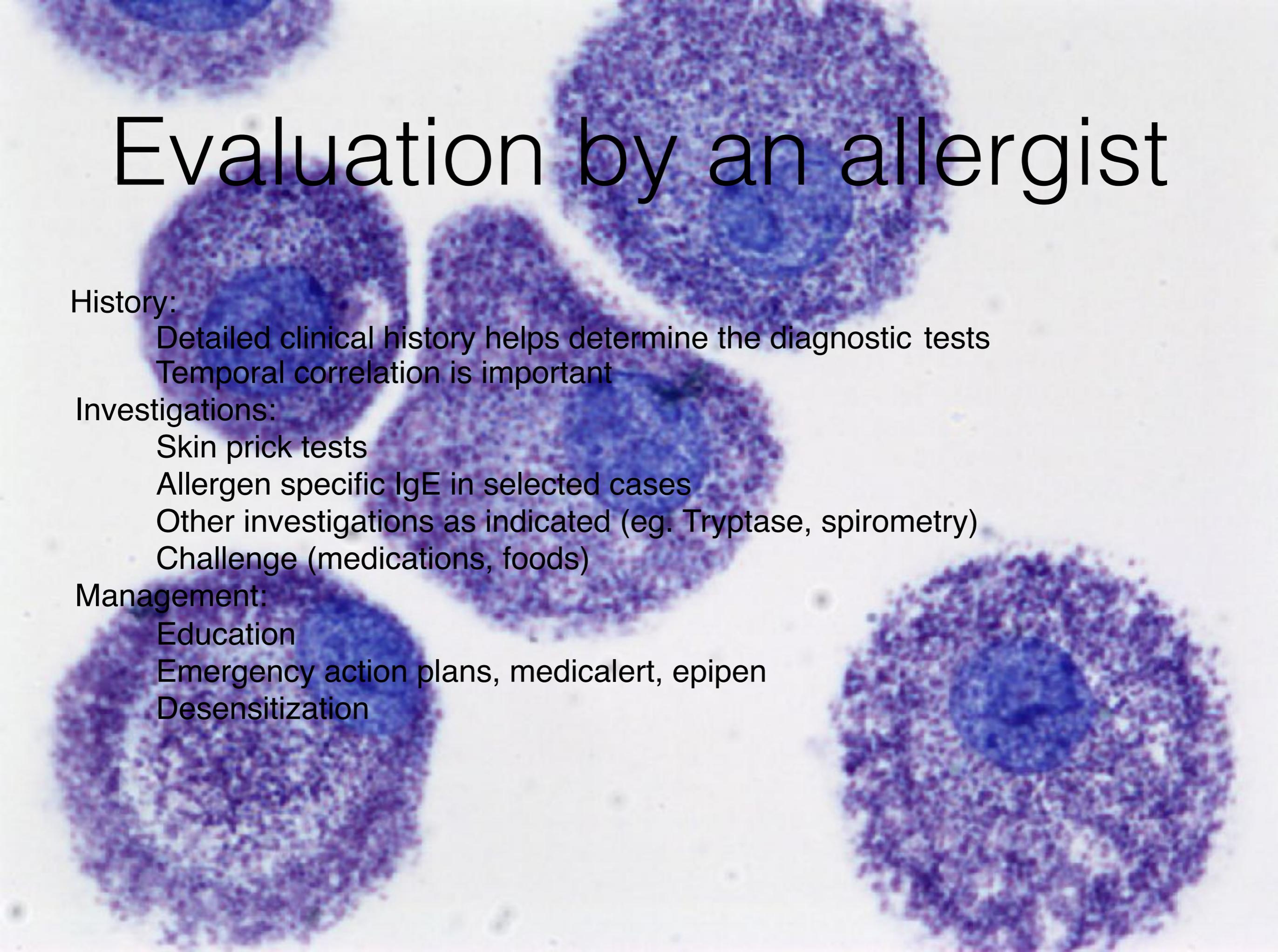
- **At least four hours advised** (but also at discretion of the emergency physician)
- Up to 20% of reactions will have a **second** reaction (biphasic) with the majority occurring within **10 hours (mean time)**
- Second-phase reactions can occur even following administration of corticosteroids



Monitoring

- Following treatment of anaphylaxis, patients should stay within close proximity to a hospital or where they can call 911 for the next **48 hours**.

Evaluation by an allergist

A microscopic image of several eosinophils, which are white blood cells. They are characterized by their large, bilobed nuclei and granules that stain a bright reddish-orange color. The background is a light, slightly grainy texture.

History:

Detailed clinical history helps determine the diagnostic tests
Temporal correlation is important

Investigations:

Skin prick tests

Allergen specific IgE in selected cases

Other investigations as indicated (eg. Tryptase, spirometry)

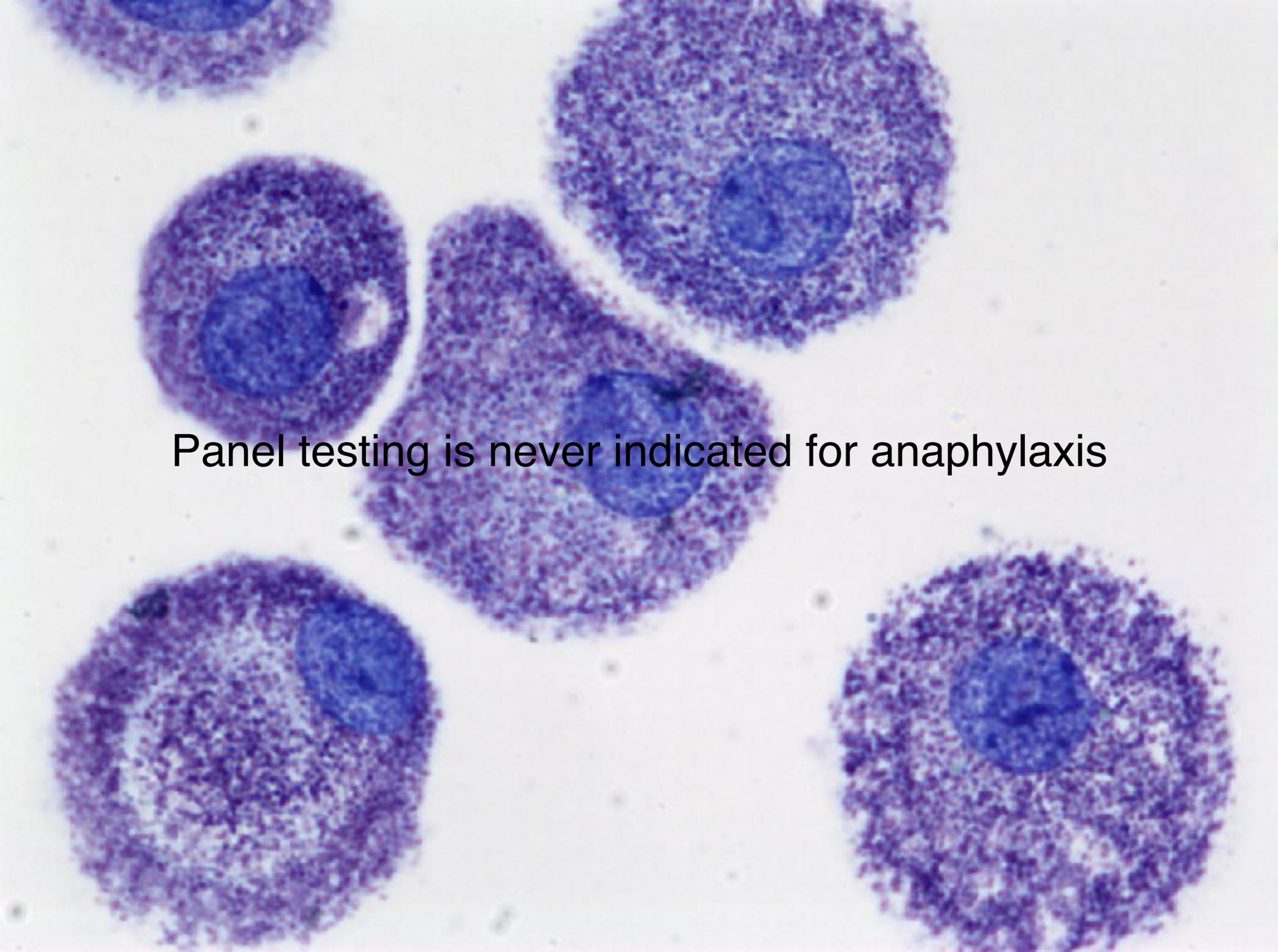
Challenge (medications, foods)

Management:

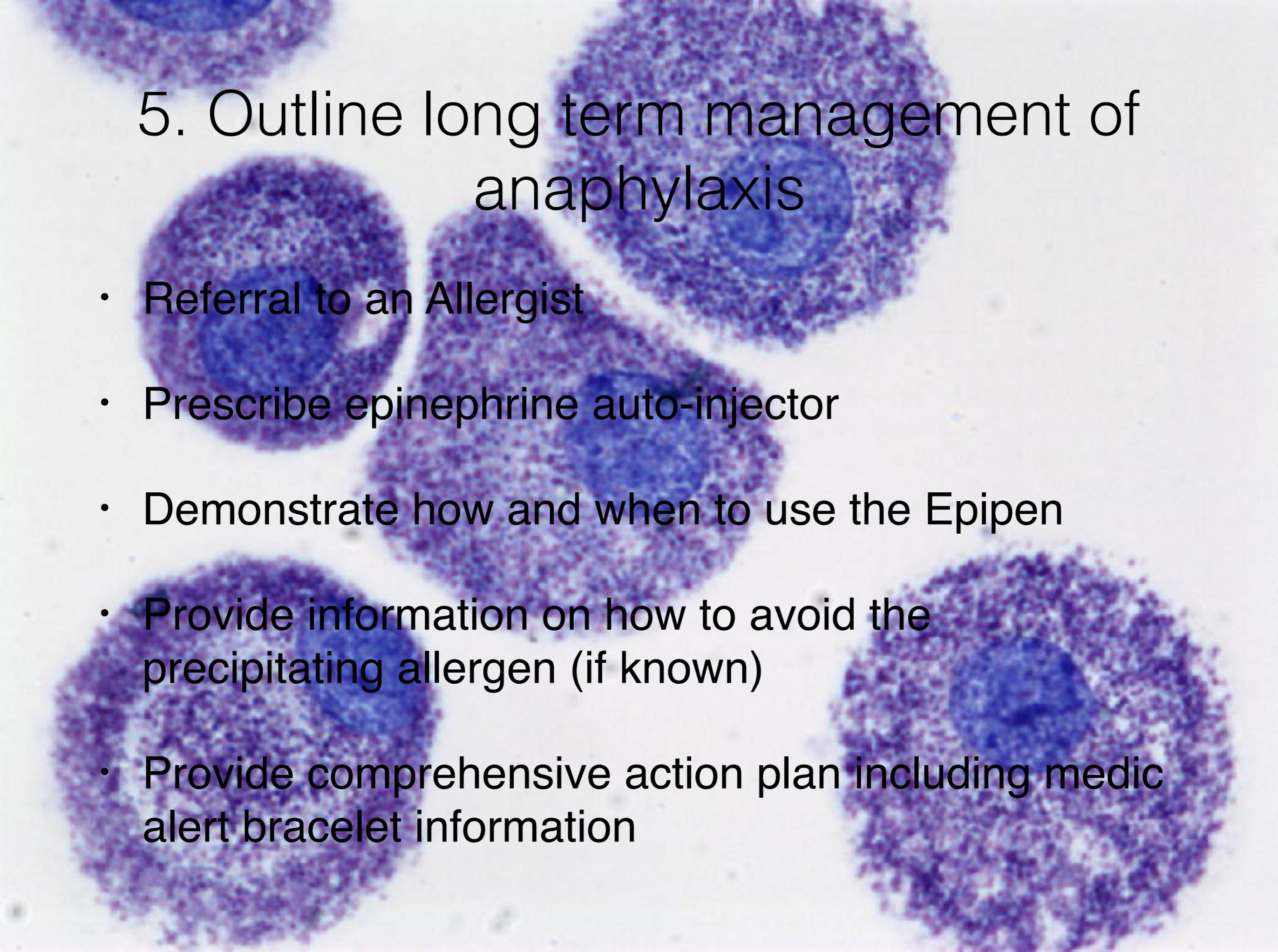
Education

Emergency action plans, medical alert, epipen

Desensitization



Panel testing is never indicated for anaphylaxis



5. Outline long term management of anaphylaxis

- Referral to an Allergist
- Prescribe epinephrine auto-injector
- Demonstrate how and when to use the EpiPen
- Provide information on how to avoid the precipitating allergen (if known)
- Provide comprehensive action plan including medic alert bracelet information

Key points

- All patients who have been diagnosed with severe allergy should be given an **anaphylaxis action plan**. The plan should be shared with family members and all potential care-providers. The plan should be reviewed with the patient at each visit.
- **All patients** at risk of anaphylaxis should be prescribed sufficient epinephrine auto-injectors to ensure there is one available to them at all times.

Key points

- There is one **epinephrine auto-injector** available in Canada, Epipen®. It's proper administration should be demonstrated to patients who have severe allergy.
- **Training devices** , which contain no medication and no needle, can be ordered at: www.epipen.ca
- Use the **teach-back method** with the training device when demonstrating **how to use** the epinephrine auto-injector. Demonstrate the administration procedure and then have the patient teach it back to you, ensuring their full understanding. Patients should be confident with the proper use of the device.

Key points

- Ensure that your patients with severe allergy are always carrying only current, **non-expired epinephrine auto-injectors, at room temperature**. Renew prescriptions regularly and educate patients to dispose of expired devices. Patient reminder programs are also available at: www.epipen.ca
- Ensure patients know that they must go to **hospital** immediately after epinephrine administration; even if they feel better, it is still an emergency.
- Patients need close monitoring after being treated for anaphylaxis.

Resources

- Anaphylaxis Canada www.anaphylaxis.ca
- Allergy/Asthma Information Association www.aaia.ca
- Asthme et Allergies Québec www.asthmeallergies.com
- Association Québécoise des Allergies Alimentaires www.aqaa.qc.ca
- Allergy safe Communities www.allergysafecommunities.ca
- Family Physician Airways Group of Canada www.fpagc.com
- Safe 4 Kids: A Site for Kids Living with Anaphylaxis www.safe4kids.ca
- Why Risk It: A Site for Canadian Youth at Risk for Anaphylaxis www.whyriskit.ca
- Food Allergy and Anaphylaxis Network (US) www.foodallergy.org
- MedicAlert Foundation Canada Inc.: www.medicalert.ca