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Anaphylaxis

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Anaphylaxis – operational definition

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- ICD code_Y78.2
- Working definition 'Serious allergic reaction that is rapid in onset and may cause death'

Anaphylaxis is defined by WHO as (1) , (2) or (3)

1) Acute onset of illness (mins-hrs) with involvement of *skin* (urticaria, pruritus, flushing) or *mucosa* (swollen, lips or tongue or uvula hypotension, collapse, incontinence) plus one of

- *Respiratory* complications – wheeze, stridor, SOB
- *Cardiovascular* complications - hypotension, collapse, incontinence

2) At least two of the following occurring acutely after **likely** allergen exposure

- Skin/Mucosa - (urticaria, pruritus, flushing: swollen, lips or tongue or uvula hypotension)
- Respiratory - wheeze, stridor, SOB
- Cardiovascular - hypotension, collapse, incontinence
- GI – abdo pains, vomiting or diarrhoea

3) Reduced BP (systolic) acutely following **known** allergen exposure

>30% reduction and < 90 for adult

Anaphylaxis Epidemiology

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- Incidence 10-50 per 100,00 person-years
- Lifetime prevalence ~0.005%
- Fatality of
  - 2 per million USA
  - 0.66 per million Australia
  - 0.33 per million UK
- Variability in cause related deaths
  - Food induced deaths-Females 10-35
  - Insect deaths – 95% in males
  - Drug induced – gender neutral but >50 year

Anaphylaxis Epidemiology

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- In children (Paed A&E)
  - 86% Food (Peanuts)
  - Medications
  - Stings
- In adults
  - Medications
  - Stings
  - Diagnostic agents
- Fatal Anaphylaxis in UK was due to
  - Medication (44%)
  - Food 31%
  - Insect 23%
- Emerging
  - OSCS
  - Biologicals*

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doi:10.1016/j.jaci.2011.01.038

Practice paper

World Allergy Organization anaphylaxis guidelines: Summary

F. Estelle R. Simons, MD, FRCPC,[a] Ledit R. F. Ardusso, MD,[b] M. Beatrice Bilò, MD,[c] Yehia M. El-Gamal, MD, PhD,[d] Dennis K. Ledford, MD,[e] Johannes Ring, MD, PhD,[f] Mario Sanchez-Borges, MD,[g] Gian Enrico Senna, MD,[h] Aziz Sheikh, MD, FRCGP, FRCP,[i] and Bernard Y. Thong, MD,[j] for the World Allergy Organization *Winnipeg, Canada, Rosario, Argentina, Ancona and Verona, Italy, Cairo, Egypt, Tampa, Fla, Munich, Germany, Caracas, Venezuela, Edinburgh, United Kingdom, and Singapore*

Anaphylaxis Symptoms

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Frequency of presenting symptoms

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.

Diagnosis of Anaphylaxis

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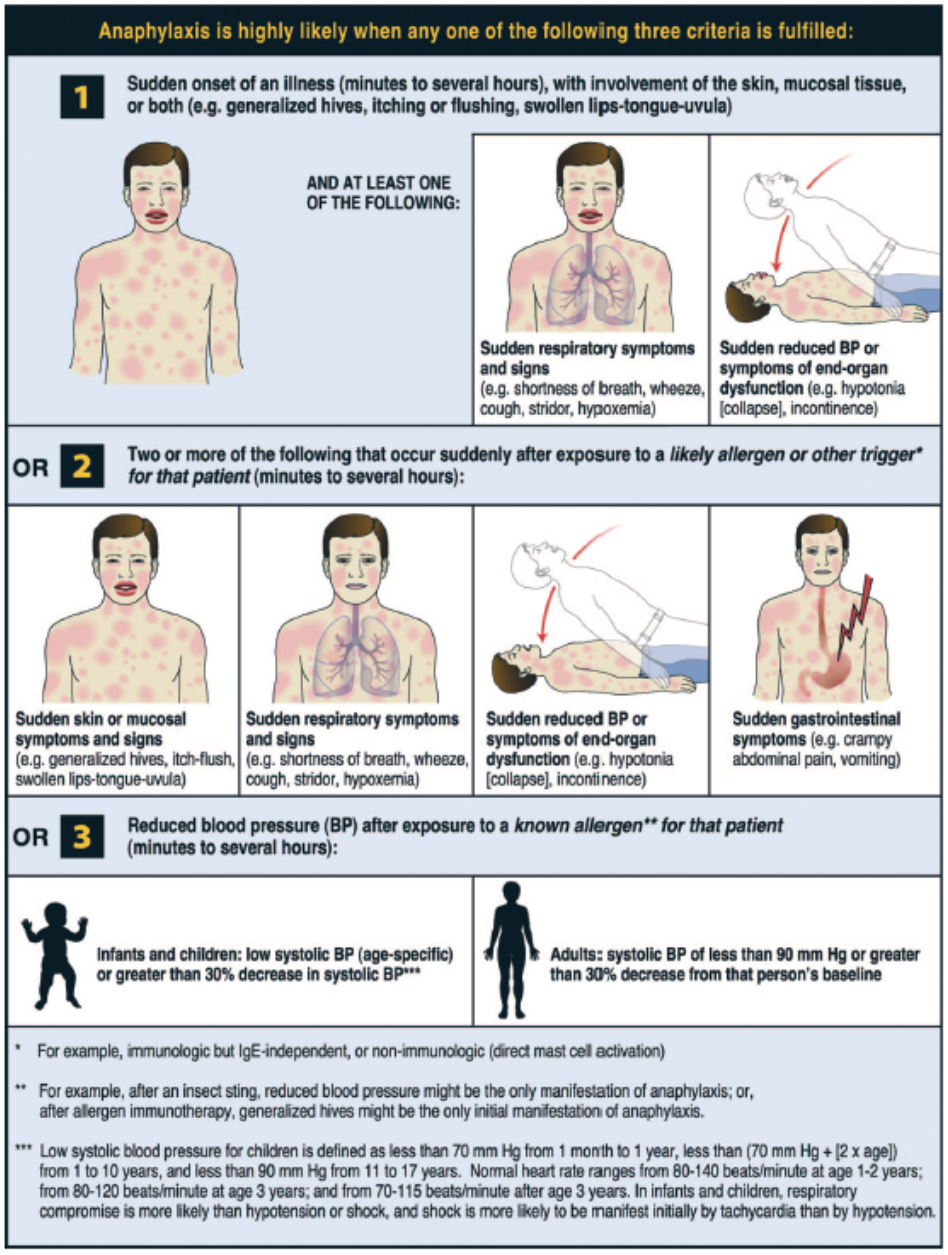

WAO Journal • February 2011

WAO Position Paper

World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis

F. Estelle R. Simons, MD, FRCPC,[1] Ledit R. F. Ardusso, MD,[2] M. Beatrice Bilò, MD,[3] Yehia M. El-Gamal, MD, PhD,[4] Dennis K. Ledford, MD,[5] Johannes Ring, MD, PhD,[6] Mario Sanchez-Borges, MD,[7] Gian Enrico Senna, MD,[8] Aziz Sheikh, MD, FRCGP, FRCP,[9] and Bernard Y. Thong, MD,[10] for the World Allergy Organization

Diff Diagnosis of Anaphylaxis

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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
Postprandial syndromes	Psychosomatic episode
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)

Endotypes of Anaphylaxis

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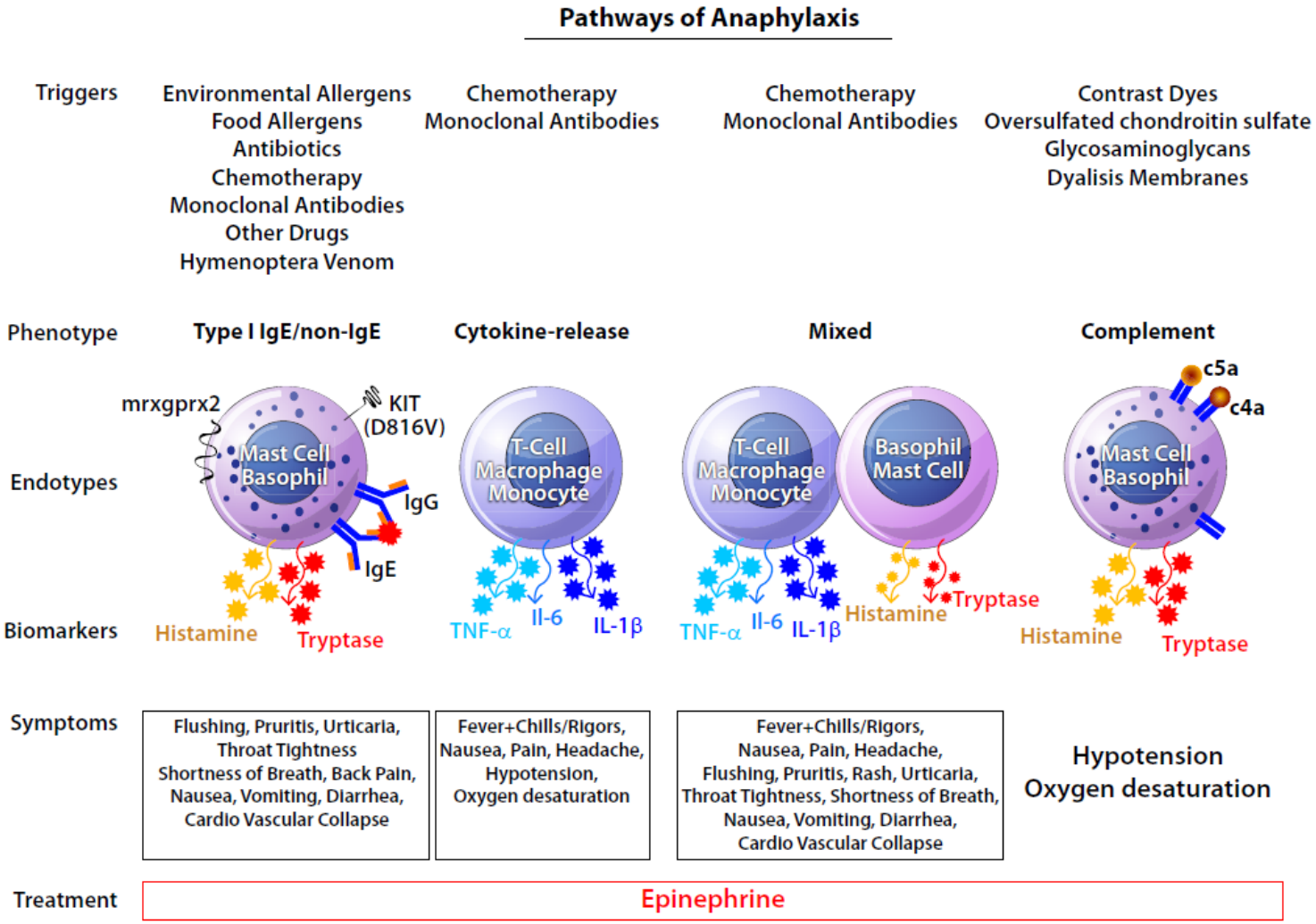

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Causes of Anaphylaxis

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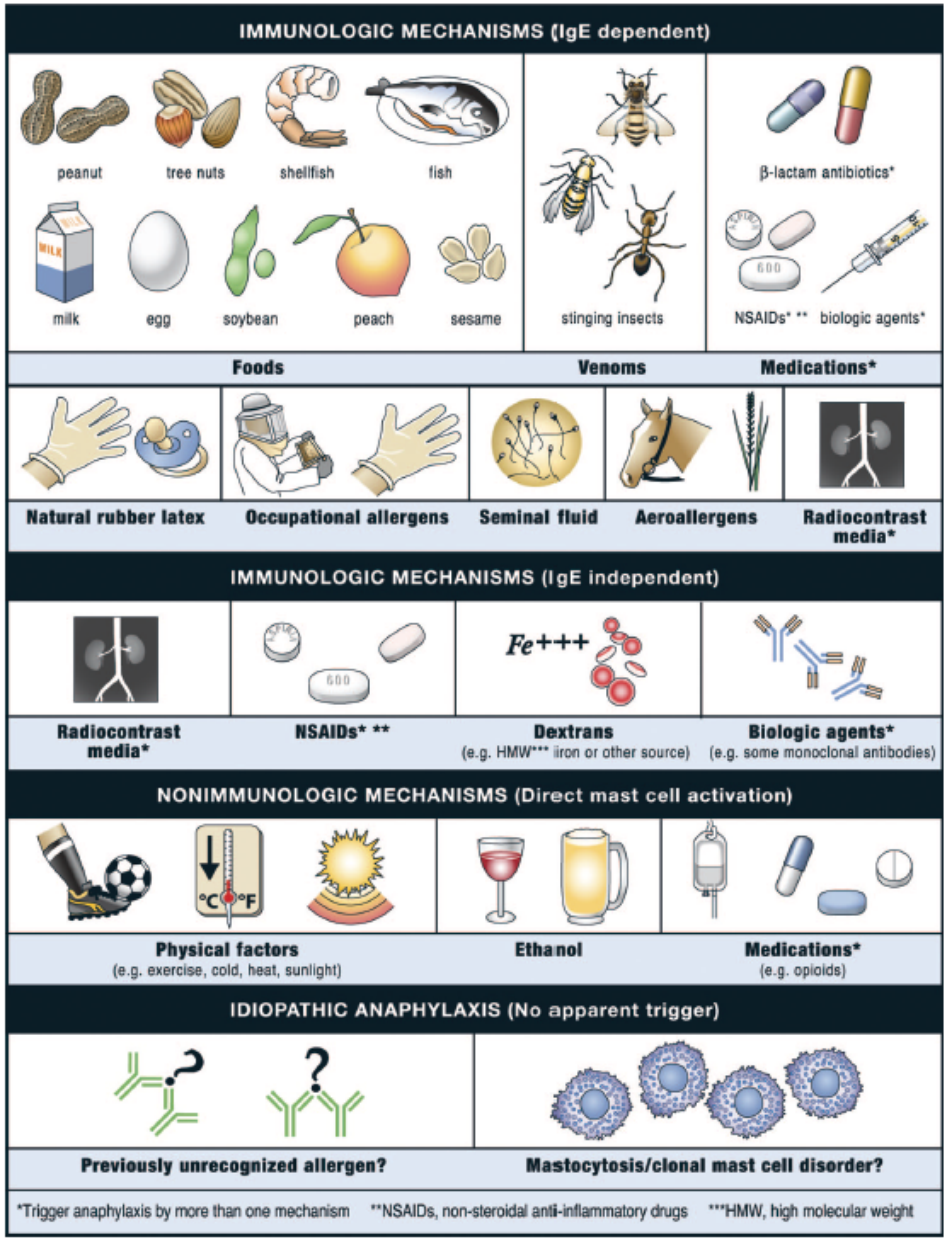

Mediators of Anaphylaxis

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Biomarkers: Skin Test
Tryptase

Mediators of Anaphylaxis

Histamine	→	Skin + Blood vessels
PGD_2	→	Brain + Flushing Vasodialation
Tryptase	→	Fibrinogen αchain C3a + C5a
Bradykinin	→	Hypotension + Swelling
Leukotrines	→	Bronchospasm + Swelling
PAF	→	Vasodilation

Anaphylaxis Pathogenesis

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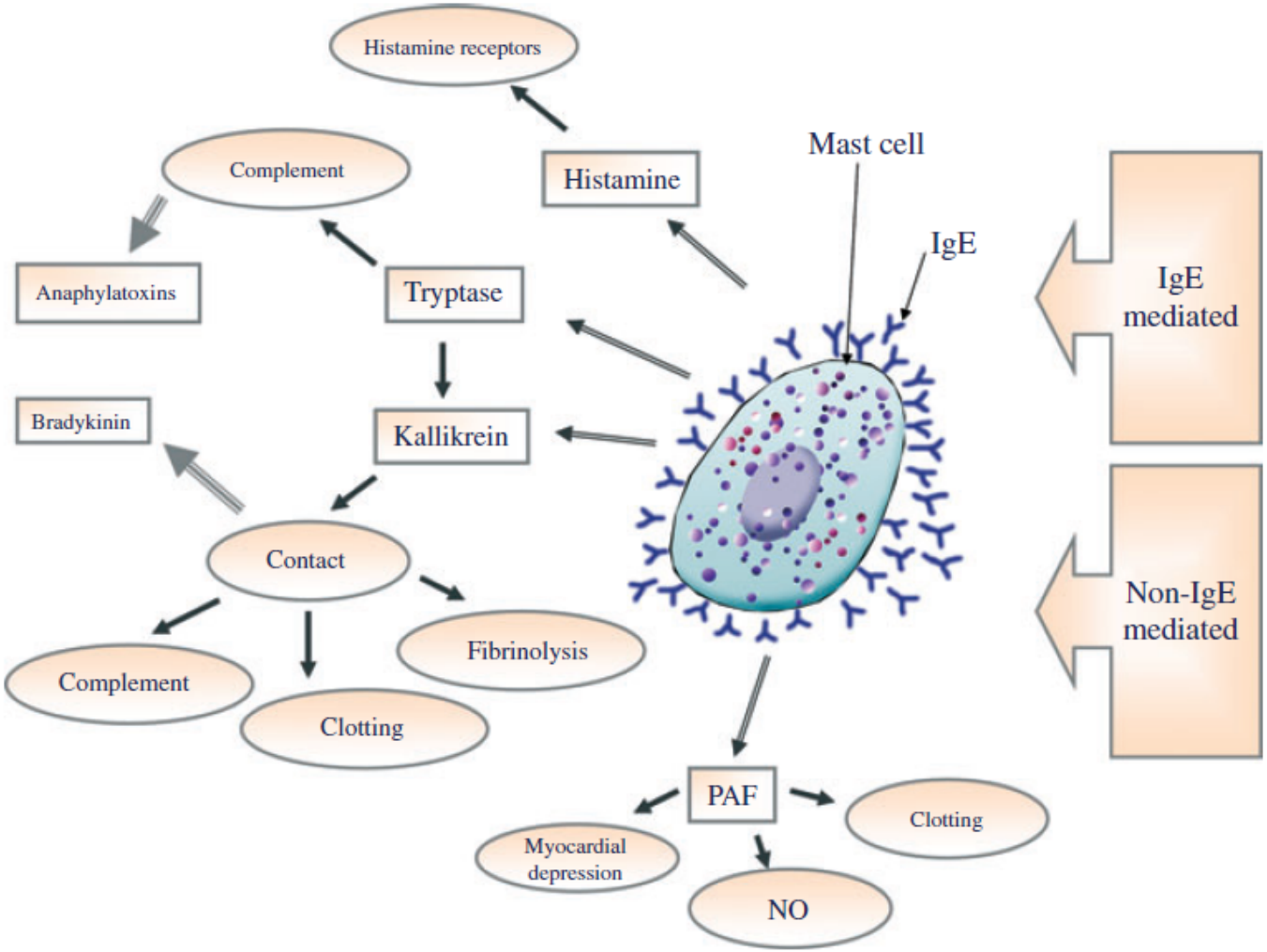

Patient Factors in Anaphylaxis

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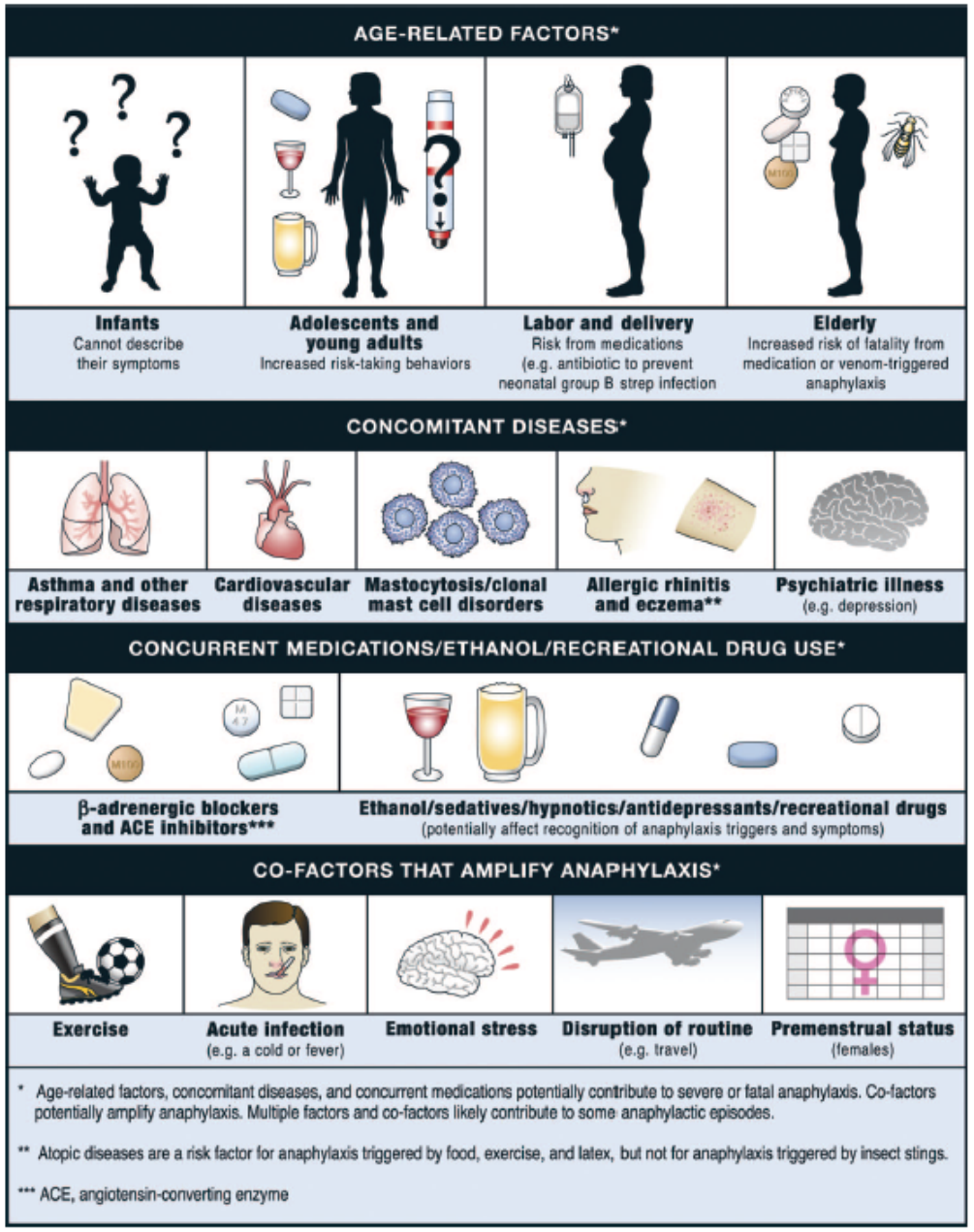

Management following Anaphylaxis

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1 **Have a written emergency protocol** for recognition and treatment of anaphylaxis and rehearse it regularly.

2 **Remove exposure to the trigger** if possible, eg. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.

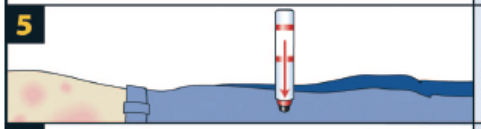
3 

Assess the patient's circulation, airway, breathing, mental status, skin, and body weight (mass).

Promptly and simultaneously, perform steps 4, 5 and 6.

4 

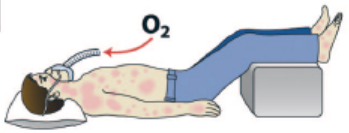
Call for help: resuscitation team (hospital) or emergency medical services (community) if available.

5 

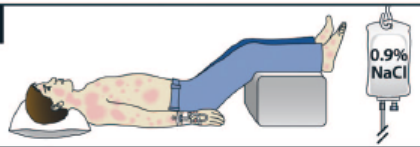
Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, maximum of 0.5 mg (adult) or 0.3 mg (child); **record the time of the dose and repeat it** in 5-15 minutes, if needed. Most patients respond to 1 or 2 doses.

6 

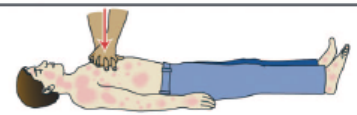
Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; **elevate the lower extremities;** fatality can occur within seconds if patient stands or sits suddenly.

7 

When indicated, give high-flow supplemental oxygen (6-8 L/minute), by face mask or oropharyngeal airway.

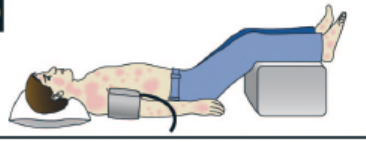
8 

Establish intravenous access using needles or catheters with wide-bore cannulae (14 - 16 gauge). **When indicated, give 1-2 litres of 0.9% (isotonic) saline rapidly** (e.g. 5-10 mL/kg in the first 5-10 minutes to an adult; 10 mL/kg to a child).

9 

When indicated at any time, perform cardiopulmonary resuscitation with continuous chest compressions.

In addition,

10 

At frequent, regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).

Adrenaline, Adrenaline and Education

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Epinephrine (Adrenaline): First-Line Medication for Anaphylaxis Treatment	
Strength of Recommendations[a]	**B-C (As Defined in Footnote)[a]**
Pharmacologic effects when given by injection[b]	At alpha-1 adrenergic receptor Increases vasoconstriction and increases vascular resistance (in most body organ systems)[c] Increases blood pressure Decreases mucosal edema in the airways At beta-1 adrenergic receptor Increases cardiac contraction force Increases heart rate At beta-2 adrenergic receptor Decreases mediator release Increases bronchodilation
Clinical relevance	Increases blood pressure and prevents and relieves hypotension and shock Decreases upper airway obstruction, eg. in larynx Decreases urticaria and angioedema Decreases wheezing
Potential adverse effects after the usual epinephrine dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution intramuscularly[d] (to a maximum of 0.5 mg [adult] or **0.3 mg** [**child**])	Pallor, tremor, anxiety, palpitations, dizziness, headache; these symptoms indicate that a pharmacologic dose has been injected
Potential adverse effects after epinephrine overdose (eg. overly rapid intravenous infusion, intravenous bolus dose, or dosing error, eg. intravenous administration of an undiluted 1:1,000 (1 mg/mL) solution[e])	Ventricular arrhythmias, hypertension, pulmonary edema; note that the heart itself is a potential **target organ** in anaphylaxis; therefore, acute coronary syndromes (angina, myocardial infarction, arrhythmias) can also occur in untreated anaphylaxis in patients with known coronary artery disease, in those in whom subclinical coronary artery disease is unmasked, and even in patients (including children) without coronary artery disease in whom the symptoms are due to transient vasospasm
Reasons why the intramuscular route is preferred over the subcutaneous route for initial treatment of anaphylaxis	Epinephrine has a vasodilator effect in skeletal muscle[c]; skeletal muscle is well-vascularized; after intramuscular injection into the vastus lateralis (mid-anterolateral thigh), absorption is rapid and epinephrine reaches the central circulation rapidly; rapid absorption is important in anaphylaxis, in which the median times to cardiorespiratory arrest are reported as 5 minutes (iatrogenic, eg. injected medication), 15 minutes (stinging insect venom), 30 minutes (food)
Reasons for apparent lack of response to epinephrine	Error in diagnosis, patient suddenly stands or sits (or is placed in the upright position) after epinephrine injection; rapid anaphylaxis progression; patient taking a beta-adrenergic blocker or other medication that interferes with epinephrine effect; epinephrine injected too late; dose too low on mg/kg basis; dose too low because epinephrine is past expiry date[f]; not enough injection force used; route not optimal; injection site not optimal; other

Adrenaline Pens -Discussion

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- Who
- When
- Why
- Which
- How many
- How much
- How long

Food Allergy

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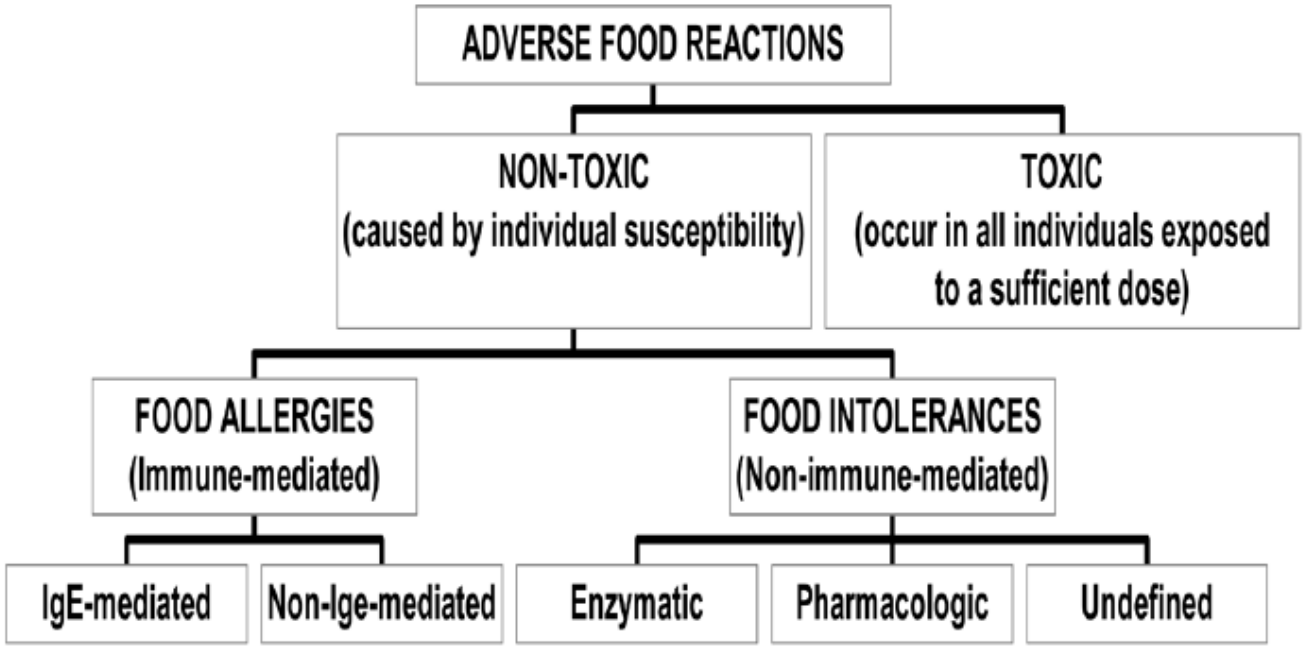

i.e. Lactase def **Vasoactive amine** **Additives**

Food allergy is appropriate when immunological mechanisms have been demonstrated

All other reactions are non allergic Food Hypersensitivity

Johansson, S. G. O., Hourihane, J. O'B, Bousquet, J., Bruijnzeel-Koomen, C. *et al.*, A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force, *Allergy* 2001, *56*, 813–824.

Overview of Food allergy problem

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- 6-8% of children have a food allergy in the first 3 years of life

Bock, S. A., Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life, *Pediatrics* 1987, *79*, 683–688.

- 2-4% of adults have food allergy

Sampson, H. A., Food allergy – accurately identifying clinical reactivity, *Allergy* 2005, *60*, 19–24.

- 85% of children outgrow food allergy in the first 5-10 years of life

Host, A., Halken, S., Jacobsen, H. P., Christensen, A. E. *et al.*, Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood, *Pediatr. Allergy Immunol.* 2002, *13*, 23–28.

Types of IgE mediated Food allergy

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- Class 1 Food allergy
  - Sensitisation to Food allergens through the Intestinal tract, typically to stable proteins
    - Egg Allergy
    - Milk Allergy
    - Peanut Allergy
- Class 2 Food allergy
  - Sensitisation to Food allergens as a consequence of sensitisation through the Respiratory tract
    - Fruit Allergy
    - Hazelnut Allergy

EU Directive 2003/89/EC for labelling of foods

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- Celery
- Cereals containing gluten
- Crustaceans
- Eggs
- Fish
- Milk
- Mustard
- Nuts (Almonds, Hazelnuts, Walnuts, Cashews, Pecan, Brazil, Pistachio, Macadamia and Queensland nuts)
- Peanuts
- Soya
- Sesame Seed
- (Sulphur dioxide and sulphites)

Insect Allergy

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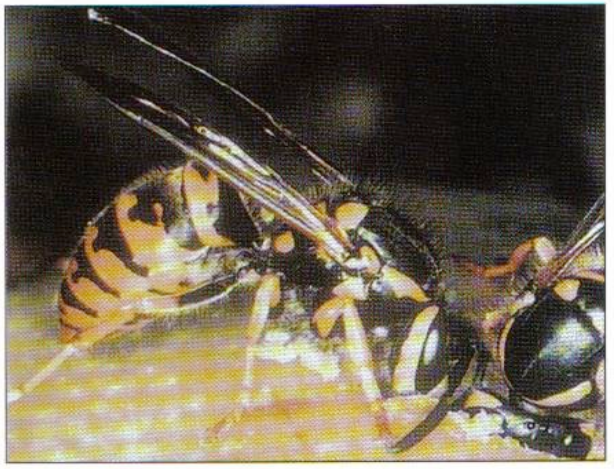
- Stinging insects belong to the order hymenoptera
- The sting is only carried by female insects
- They tend to sting only in defence
- Apids ('Bees') have a barbed sting and die after stinging
- Vespids ('Wasps') may sting repeatedly



Hymenoptera Insects

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- Apids
- Domestic honeybees are relatively docile
- The majority of stings occur in Beekeepers
- ‘Killer bees’ are African-European’ hybrids that escaped in to the wild in Brazil
  - They have a tendency to swarm and sting in large numbers with little provocation
- Bumblebees do not usually sting and show very limited cross reactivity to honeybee sting reactions

- Vespids
- These are scavengers of food
- Yellow jackets (‘UK wasps’) are highly aggressive {Vespula germanica}
- Yellow and White faced hornets are present in the North America and are nesting Yellow jackets.
- True Hornets (Vespa genus) include the European Hornet (Vespa crabro)
- Paper wasps have a distinctive ‘wasp waist’ and dandling legs

Hymenoptera Insects

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Vasoactive Amines

- Histamine, Dopamine, noradrenaline, acetylcholine and kinins

- Allergens
  - Phospholipase A is the major allergen in Honeybee venom
  - Antigen -5 is the major allergen in Vespid venom
- Cross reactivity of venom components
  - Within the Apid family there is limited cross reactivity
  - Within the Vespid family there is extensive cross reactivity
  - Between different families there is limited cross allergenicity
- Mortality
  - 5 /year 1 per 10 million annually
- Lethality
  - 1 fatality in every 100,000 insect sting allergic patients per year
- Commercial venoms
  - Protein extracts from honeybee, yellow jacket or mixed Vespula
  - Honeybee venoms are standardised against Phospholipase A
  - Vespid venoms are standardised against hyaluronidase
  - The standard dose is 100ug of each venom, equivalent to the protein content of 2-4 stings (Honeybees consistently @ 50ug, with vespids at 2-20ug/sting)

Drug Allergy

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Neuromuscular blockers	**Hypnotics**
Suxamethonium	Propofol
Atracurium	Midazolam
Mivacurium	**Colloids**
Rocuronium	Gelofusin
Vecuronium	**Opioids**
Antibiotics	Fentanyl
Penicillin	**Miscellaneous**
Amoxycillin	Chlorhexidine
Cephalosporins	Lignocaine
Quinolones	Betadine

Diverse Drivers of Perioperative Anaphylaxis

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TABLE E7. Agents frequently implicated in perioperative anaphylaxis and probable mechanisms of adverse reactions

Agent	IgE-mediated mast cell activation	Complement-mediated	Direct mast cell activation
Muscle relaxants	+	−	+
d-TubocurarineSuxamethonium (succinylcholine)			
Pancuronium			
Atracurium			
Vecuronium			
Hypnotics-barbiturates	+	+	+
Thiopental			
Methohexitone			
Nonbarbiturate hypnotics	±	+	+
Propofol			
Althesin			
Opioids	±	−	+
Morphine			
Buprenorphine			
Fentanyl			
Plasma expanders	−	+	+
Dextran			
Hydroxyethyl starch			
Protamine	+	+	+
Radiocontrast media	−	+	+
Latex	+	−	−

Unusual Causes of Unexplained Anaphylaxis

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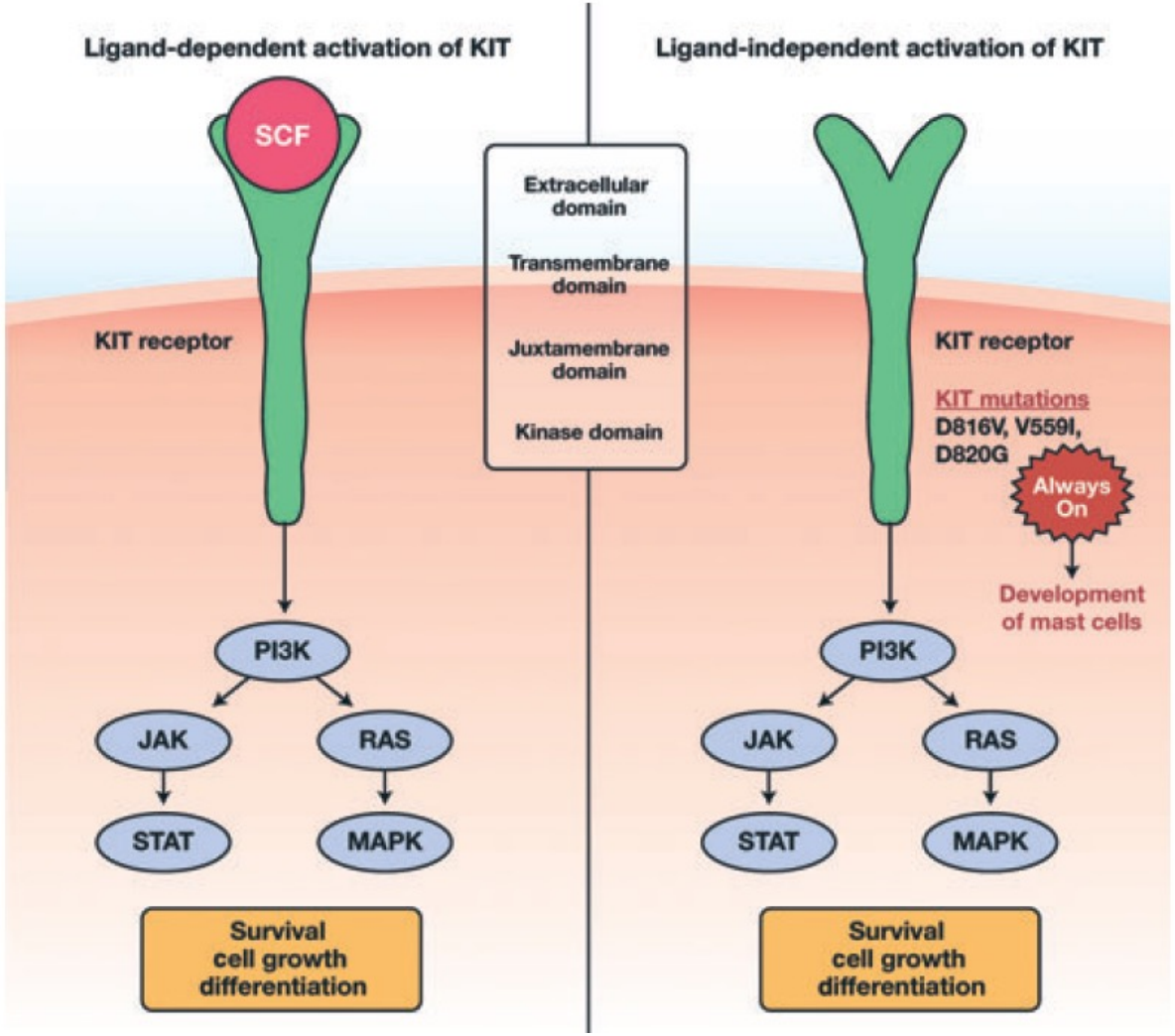
- Mast Cell Activation Disorders
  - No evidence of mastocytosis but minor criteria
    - Symptoms typical of those produced by mast cell degranulation
    - Substantial increase in mast cell mediators within 4 hours of anaphylactic event (20% increase +2ng/ml)
    - Response to agents that attenuate mast cell mediator effects on target organs
- Mastocytosis
  - A clonal population of mast cells often with a 816A>V pathogenic variant in the cKIT receptor

Mast Cell is switched on with cKIT variant



Mast Cell Activation Syndromes

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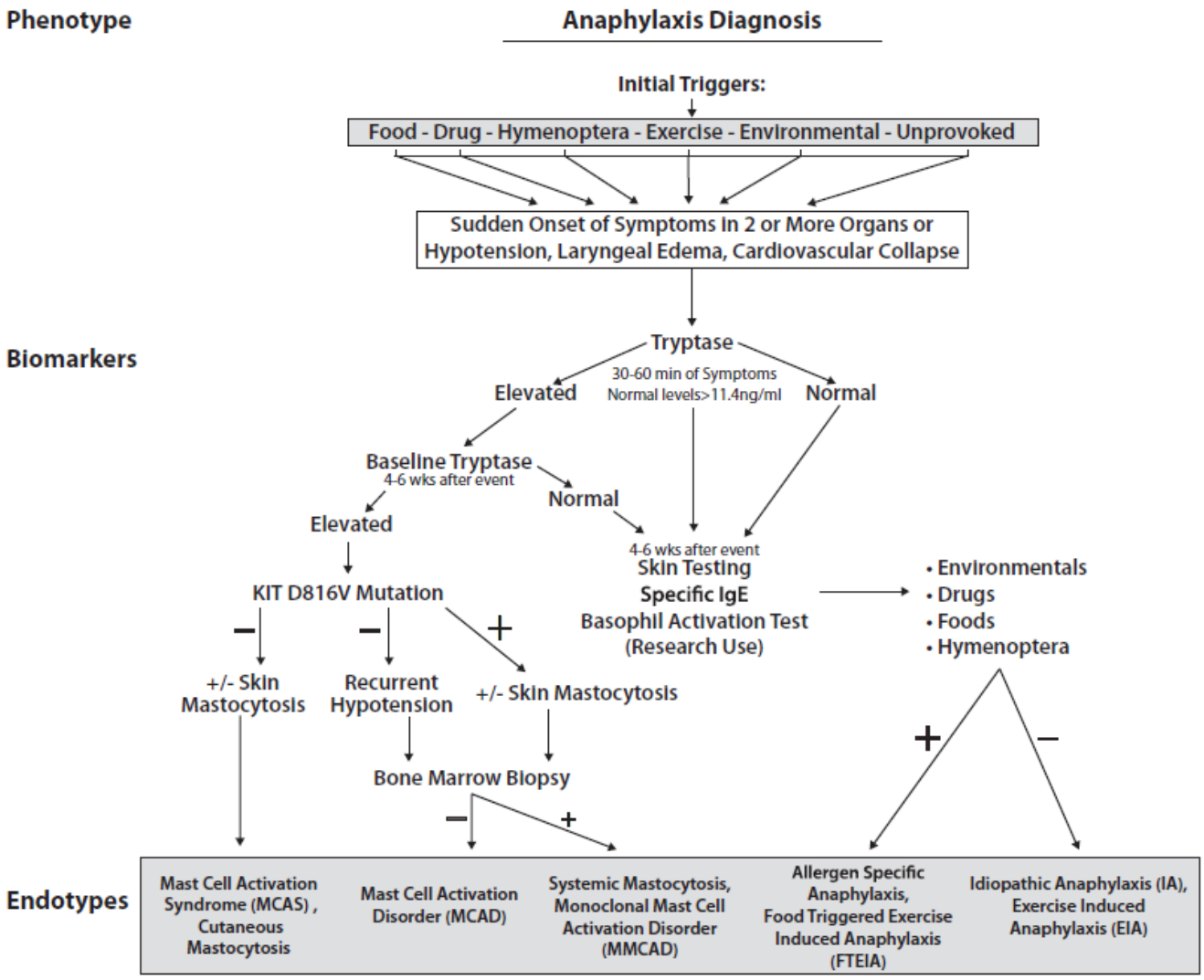

FIG 2. Algorithm for the diagnosis of anaphylaxis. *MCAS*, Mast cell activation syndrome.

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Unusual Causes of Unexplained Anaphylaxis

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- Galactose-α-1,3-galactose (α-gal)
  - Anaphylaxis triggered by food or drugs through the same pathway
    - Oligosacharide that is a blood group antigen
    - IgE antibodies first identified in the context of Cetuximab , a monoclonal antibody for treating Colon cancer, with first dose anaphylaxis .
    - Cetuximab anaphylaxis was geographically distinct in US and only with one companies product.
    - Hypersensitivity was common in areas where tick bite allergy was present due to a cross reaction between oligosaccharide on tick and the manufacturing process of Cetuximab.

Unusual Causes of Unexplained Anaphylaxis

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- Galactose-α-1,3-galactose (α-gal)
  - Extension to Food
    - α-gal is expressed in non-primate mammalian meat
    - Studies in 2009 identified that unexplained anaphylaxis to beef, lamb ad pork was associated with IgE to α-gal.
    - Unusually the anaphylaxis episodes began up to 6 hour after the ingestion of the food
  - Tick Causation
    - The Lone Star tick was implicated in the US and other tick in different parts of the world
    - Serum specific IgE test now available

Unusual Causes of Unexplained Anaphylaxis

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- Exercise Associated Disorders
  - Exercise-induced anaphylaxis (EIA)
    - Recognised in early 1980's with presentations of flushing, urticarial, progressing to angioedema.
    - Settles with reduced exercise
    - May be premedicated
  - Food-dependent exercise-induced anaphylaxis (FDEIA)
    - The above only in the presence of certain foods typically ingested within 4 hours of exercise
    - Many foods implicated including Wheat, shellfish and nuts

Unusual Causes of Unexplained Anaphylaxis

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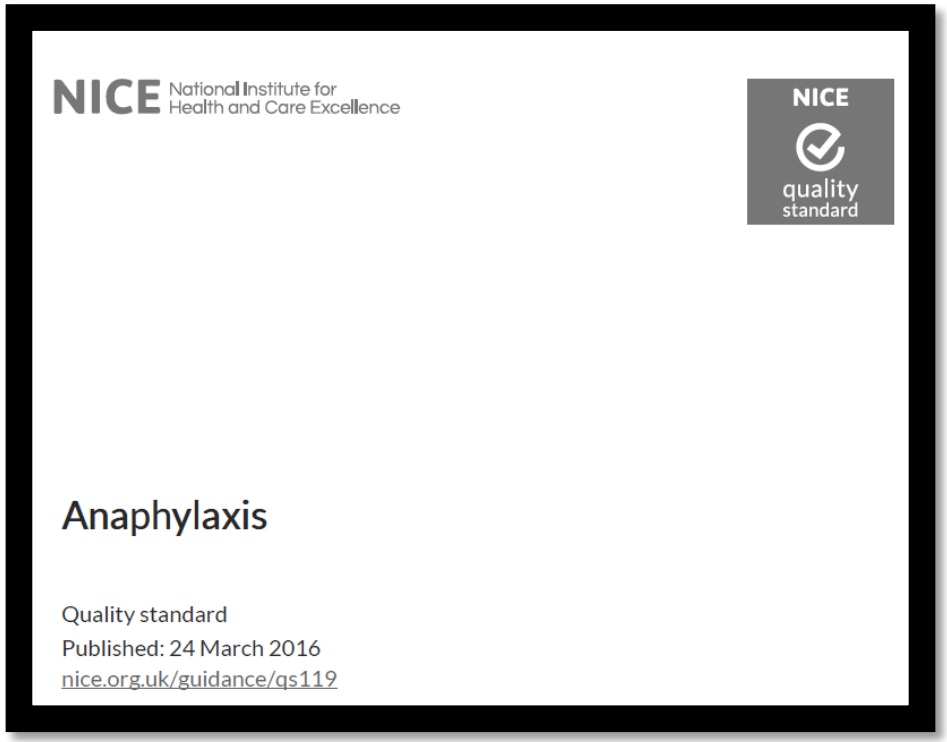
- Exercise Associated Disorder
  - Food-dependent exercise-induced anaphylaxis (FDEIA)
    - This disorder can be influenced by the concomitant usage of NSAID or alcohol, which affect allergen absorption
    - Similarly they may synergise with exercise to lower activation threshold for sensitised mast cells
    - Wheat Dependent EIA is most commonly described FDEIA
    - This is secondary to a protein component of gluten known as Omega-5 gliadin
    - Can be diagnosed by SPT to high gluten flour or by specific IgE testing to omega-5 gliadin
    - Newer concepts of Food allergy have considered WDEIA as a form of 'augmentation factor-triggered food allergy'

Guideline on Management



- 4 Quality statements
- Referral to Specialist Allergy services after emergency treatment
- Education in adrenaline auto-injector use
- Specialist assessment for Venom Immunotherapy
- Ongoing training in adrenaline auto-injector use

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Summary – Key Points

- Anaphylaxis is the most severe of the allergic reactions
- Acute management and treatment depends on early recognition and prompt use of epinephrine
- Common triggers include food, venoms, drugs and exercise with ~30% idiopathic
- Diagnosis relies on skin testing, IgE measurement, food and drug testing