Anaphylaxis update

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Allergy Immunology Section

Objectives

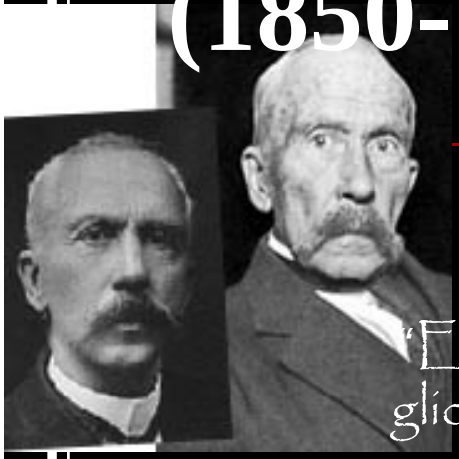
- Definition and epidemiology
- Causes and predictors
- Mechanisms and mediators
- Implications for diagnosis and treatment
- Conclusions

History

- Pharaoh Menes died from an anaphylactic reaction to a wasp sting 2500 AC
- 1900: C Richet and PJ Portier set out to develop an antitoxin to the venom of the Portuguese man-of-war
- Instead, they discovered the reaction they termed anaphylaxis
  - from the Greek for immunity or protection

Simons F.E.R. Ancestors of allergy 1994

Charles Richet (1850-1935)

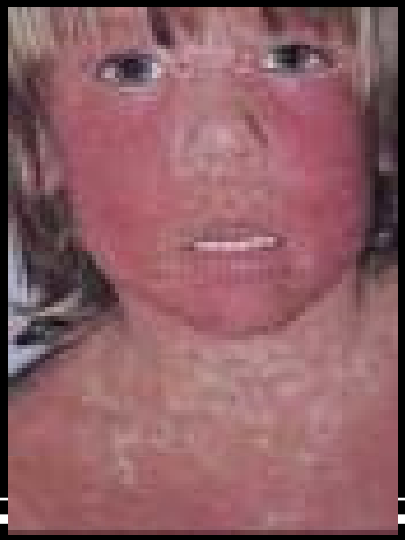


Premio Nobel 1913

"El veneno de los tentáculos de las Actinias, en solución glicerinada, es mortal por inyección endovenosa en el perro, cuando la dosis inyectada sobrepasa los 0.15 cm3 por kilogramo. Cuando la dosis se encuentra entre 0.15 cm3 y 0.30 cm3 la muerte sobreviene en 4 o 5 días. Con dosis inferiores a 0.15 cm3, el animal, salvo algunas excepciones, sobrevive después de un período de alteraciones que duran 4 o 5 días. Pero si, en lugar de inyectar animales normales, se inyectan perros que hayan recibido 2 o 3 semanas antes una dosis no mortal, entonces las dosis de 0.08 cm3 a 0.25 cm3 conducen rápidamente a la muerte"

Incidence and mortality

- Incidence unknown
  - Simons (1%)
  - US 84,000/yr
  - 1 case per 1,500 patient
  - overall incidence rate of 49.8 cases per 100,000person-years
- Mortality
  - 1 fatality for every million hospitalizations
  - 154-840 death per year in the USA



Decker W, et al.JACI 2008

Problem

- ALTHOUGH more than 100 yr have passed since **anaphylaxis** was first reported, clinicians struggle with the definition and mechanisms of anaphylaxis

Definition

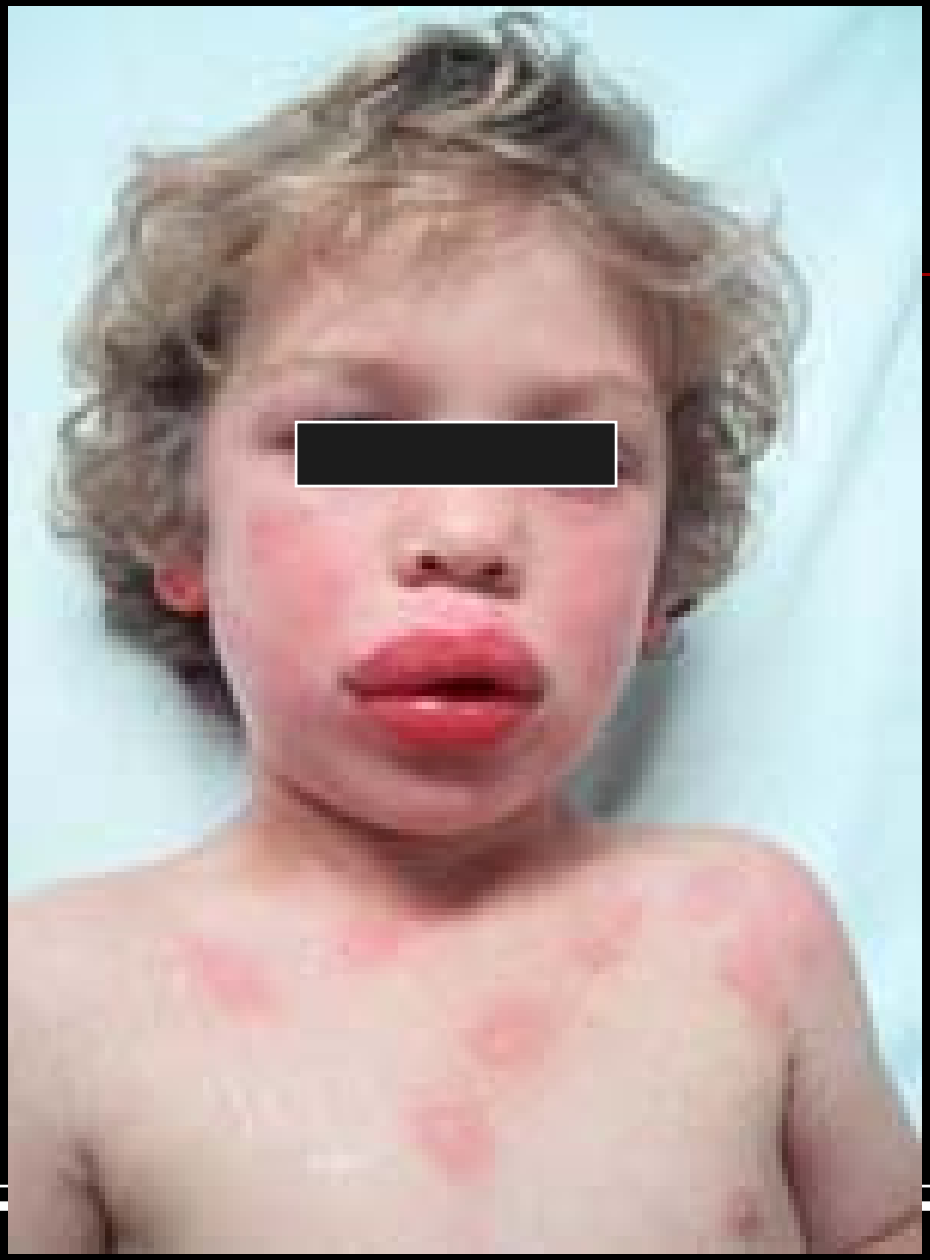
- Anaphylaxis is an acute life-threatening reaction that results from the sudden systemic release of mast cells and basophil mediators caused by an IgE-mediated reaction

Definition

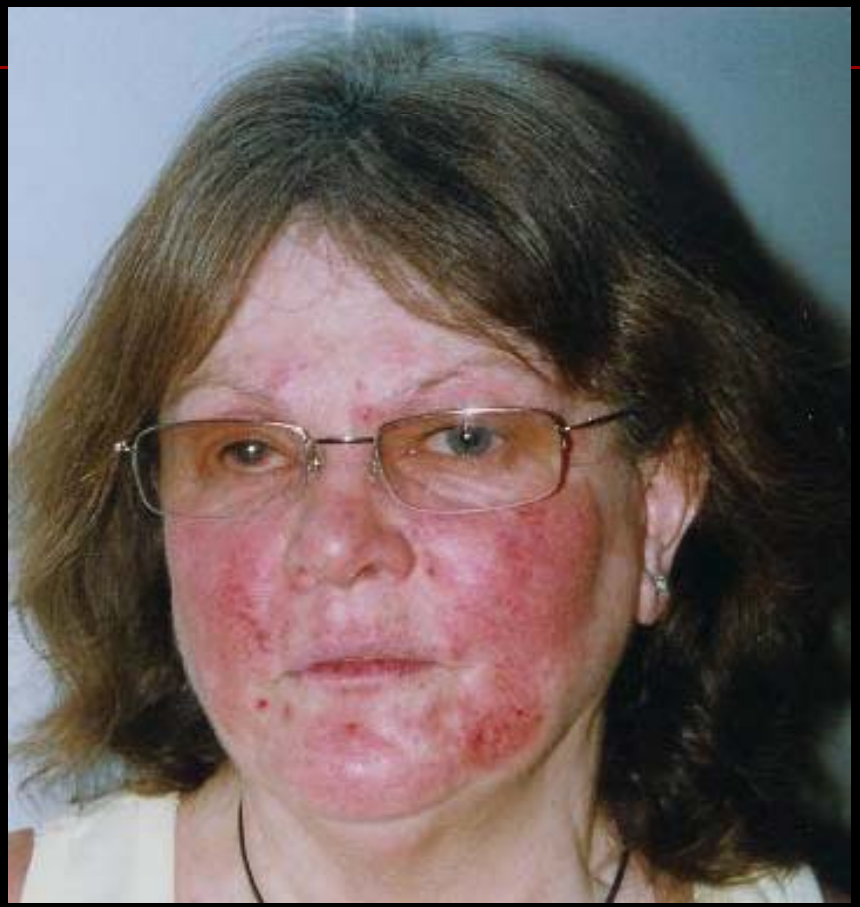
- Anaphylactoid reactions are defined as those reactions that produce the same clinical picture as anaphylaxis but are not IgE mediated.
- Where both IgE-mediated and non–IgE-mediated mechanisms are a possible cause, the term “anaphylactic” is used.

Criteria for diagnosis

- Anaphylaxis is highly likely when any one of the 3 criteria are fulfilled
  - Acute onset of illness with involvement of skin, mucosa or both AND AT LEAST ONE OF: respiratory compromise or reduced blood pressure
  - 2 or more rapidly after exposure of a likely allergen for the patient: skin, respiratory, hypotension or gastrointestinal symptoms
  - Reduced BP after exposure to known allergen

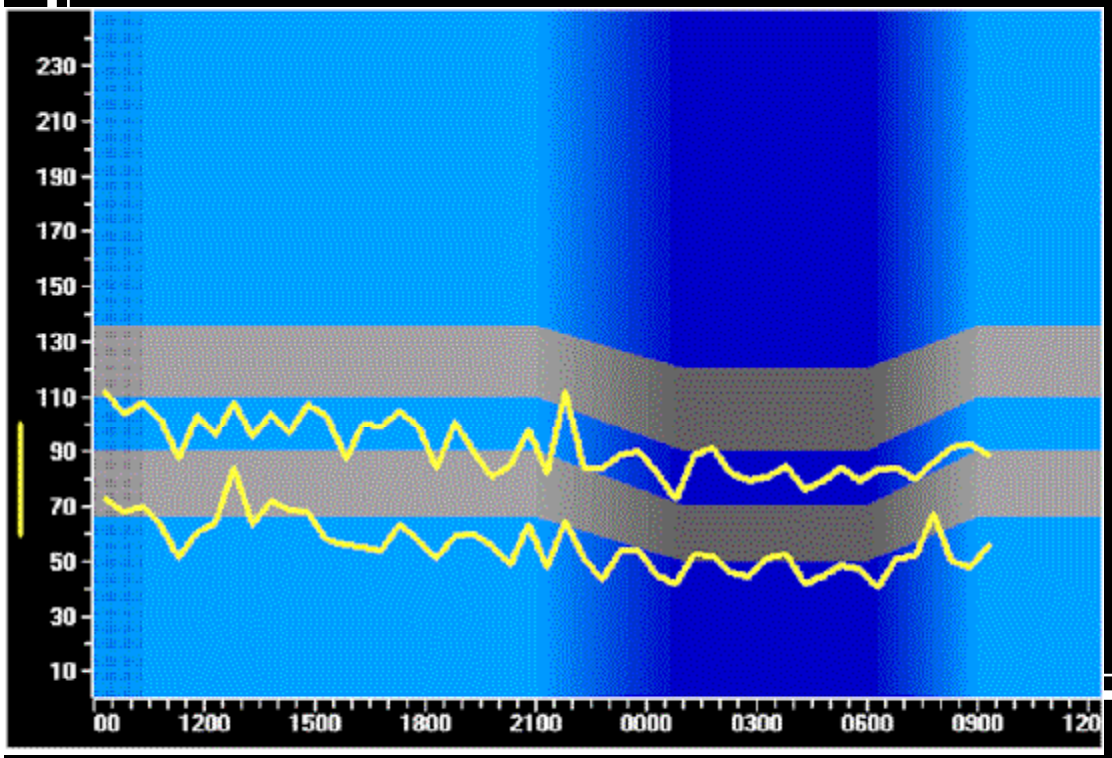


- Acute
- Skin /mucosa
- Respiratory or BP compromise



- Likely allergen
- 2 targets: skin, mucosa, gastrointestinal, respiratory, blood pressure

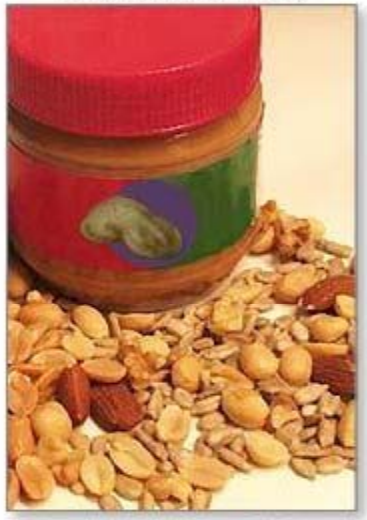
- Known allergen
- Hypotension

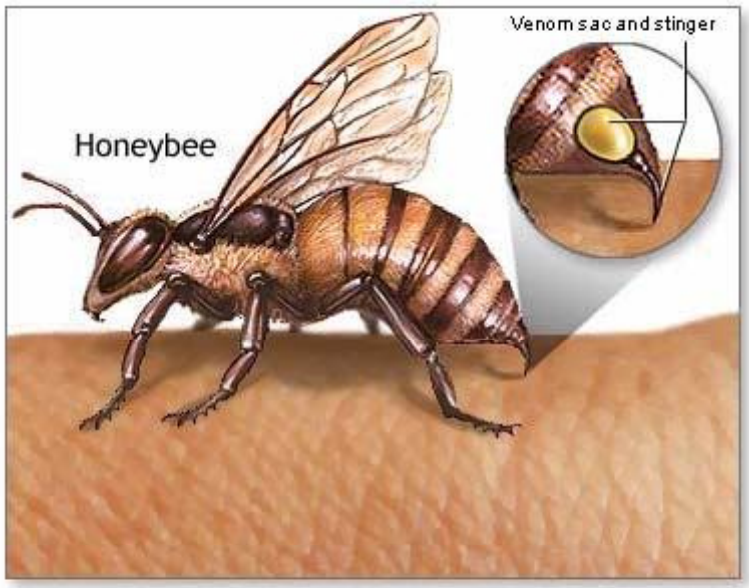


Causes

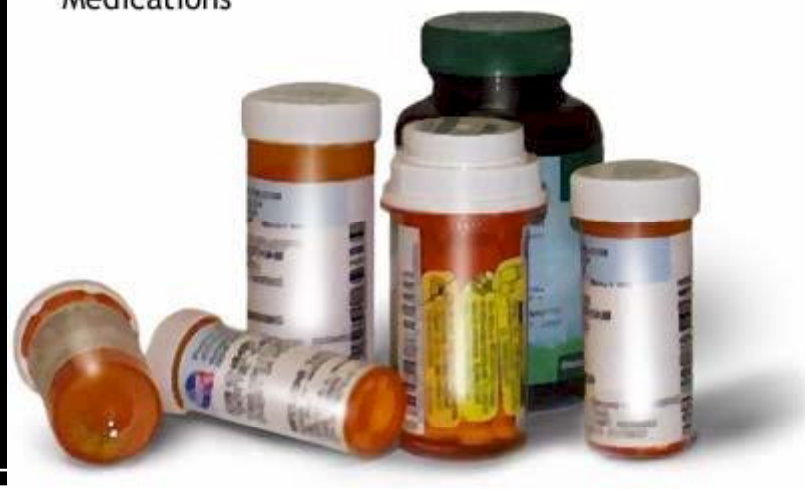
Shellfish

Peanuts and nuts

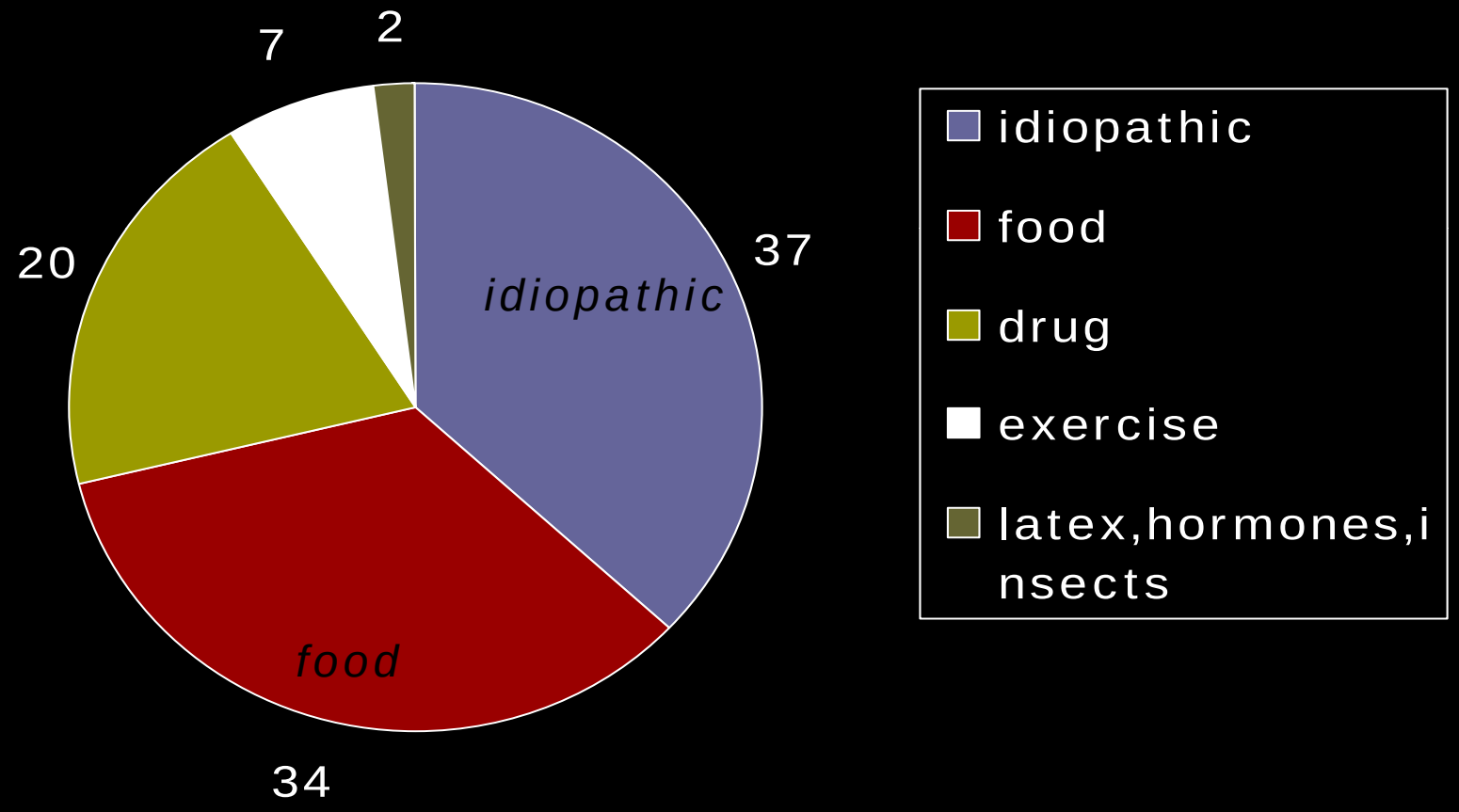




Medications

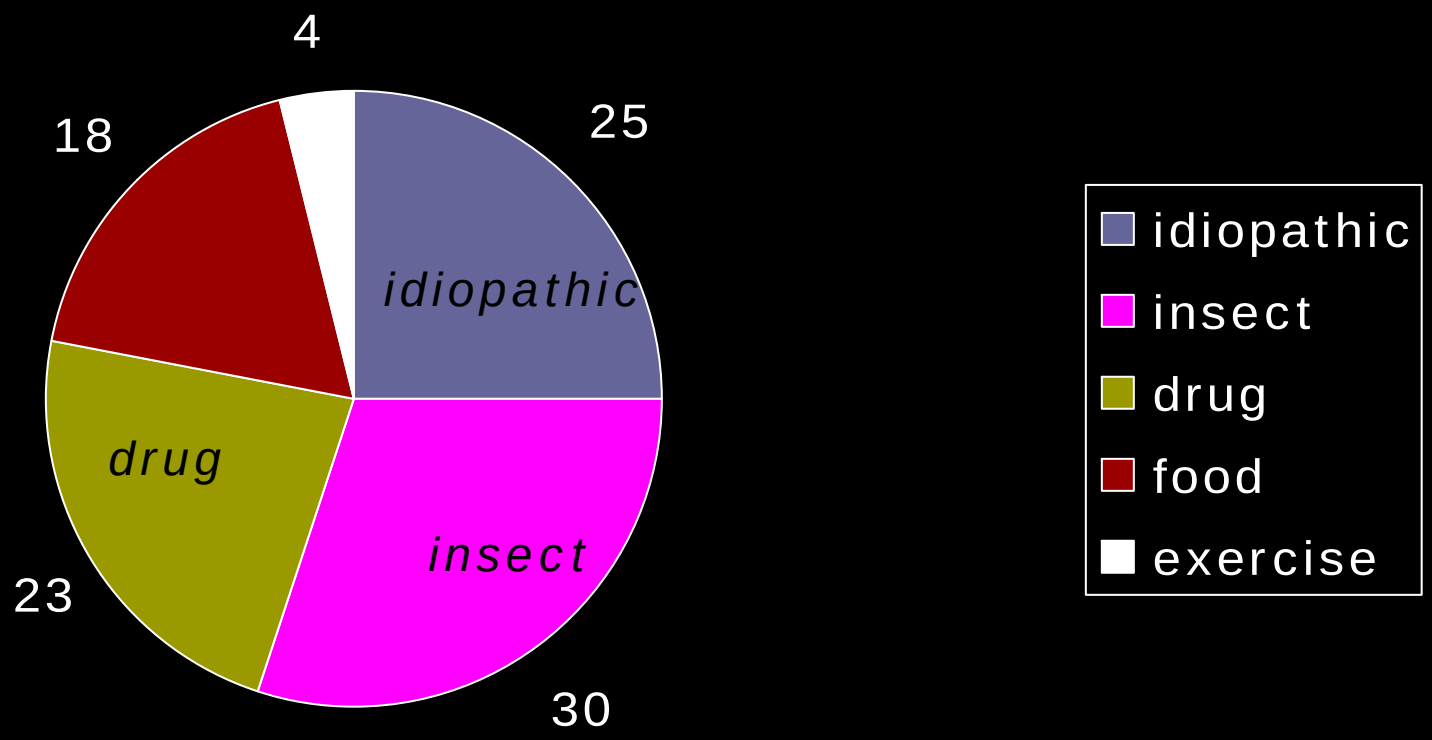


US experience



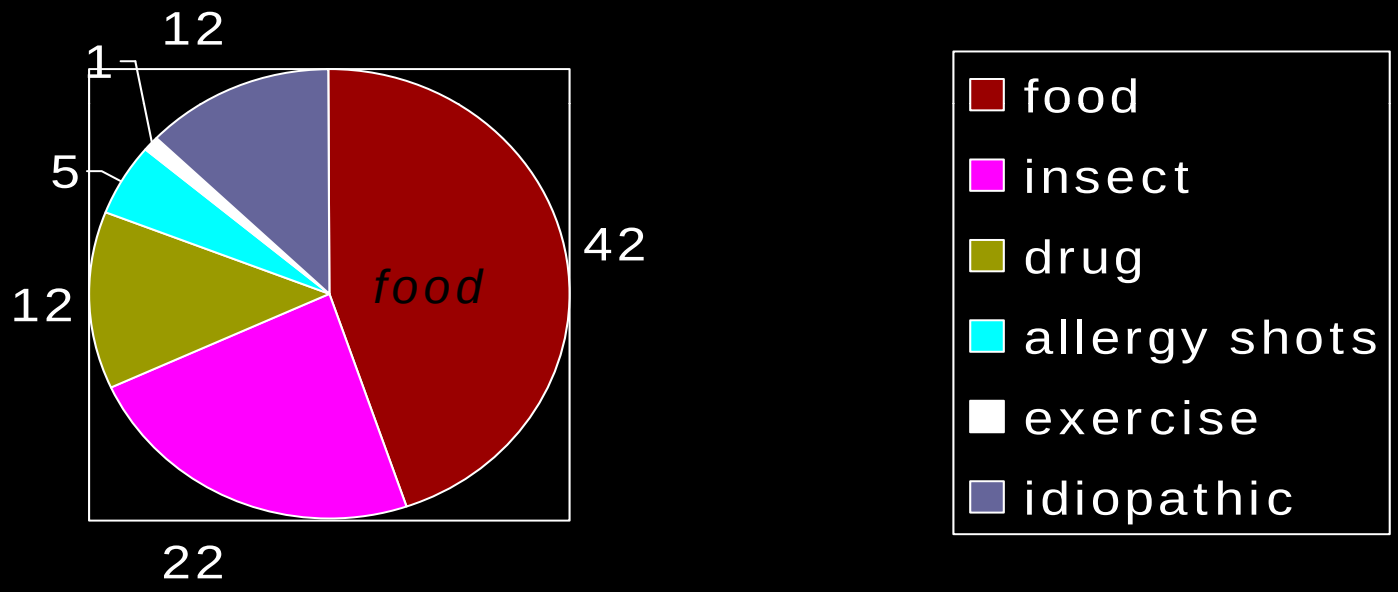
Kemp SF;Arch Intern Med;1995

UK experience



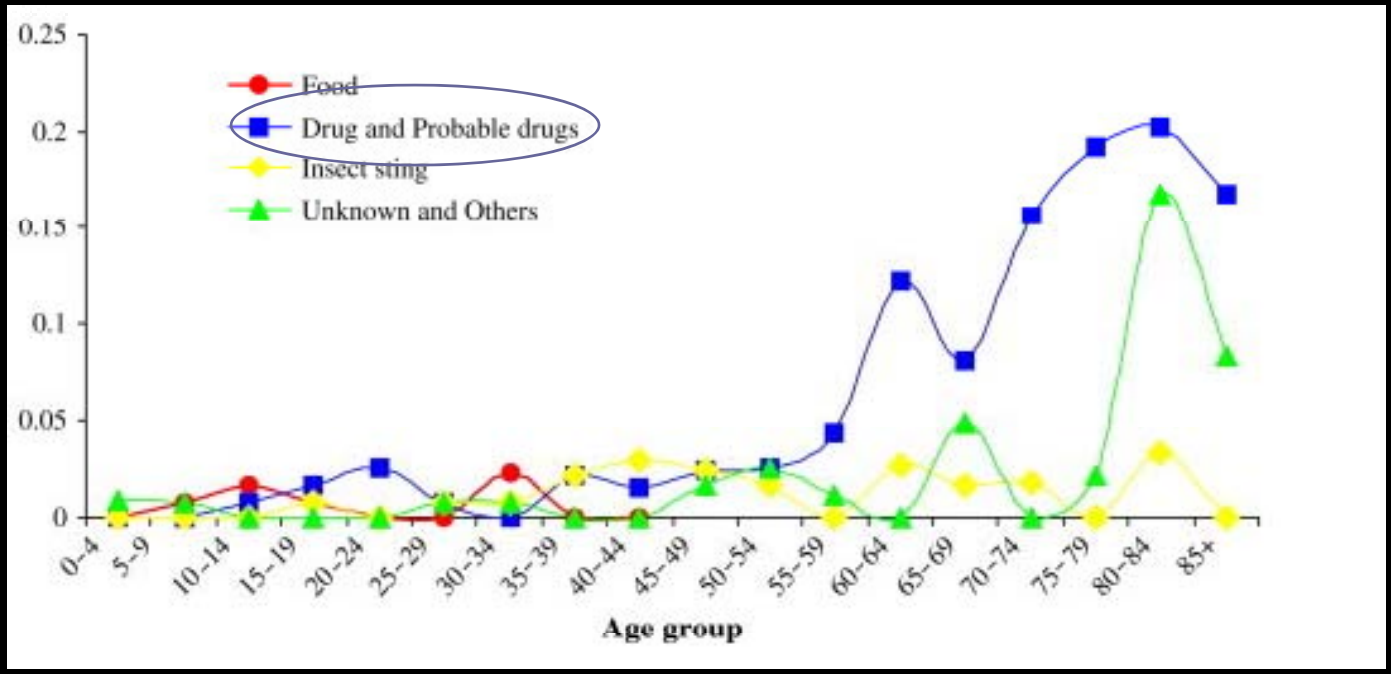
Brown S, JACI, oct 2004

Pediatric experience



Bohlke k, JACI 2004

Australia experience



Fatalities due to Drug induced

Liew et al JACI 2009

Pediatric experience

- Chart review of pediatric patients of HMO from 1991 through 1997
- Using the most specific codes for anaphylaxis, an incidence rate was 10.5 per 100,000 person-years
- inclusion of likely cases of anaphylaxis increased the incidence estimate to 68.4 per 100,000 person-years
  - the highest rate of anaphylaxis was in the 15- to 17-year age group
  - food was the most common trigger: nuts

Bohlke K.J Allergy Clin Immunol (2004)

Severity: What we should be aware of

Severity of reaction

- 315,110 presentations to the Royal Hobart Hospital ED from October 1990 to December 1999 were considered
- 1149 satisfied inclusion criteria
  - Five hundred forty-four (47%) were male.
  - Ages ranged from 0 to 96 years, with a median of 29 years

Brown S, JACI, oct 2004

Predictors of hypotension

Sx	odd ratio	p
Incontinence	13 (1.2-143)	.033
Collapse	6.3 (3.1-13)	<.001
Diaphoresis	4.0 (1.9-8.5)	<.001
Cyanosis	3.4 (1.3-8.4)	.010
Vomiting	2.9 (1.5-5.6)	.002
Dizziness	2.7 (1.4-5.3)	.003
Dyspnea	2.1 (1.2-3.7)	.008
Nausea	2.2 (1.1-4.2)	.018

Brown S, JACI, oct 2004

Predictors of cyanosis

Sx	odds ratio	p
Confusion	9.9 (1.3-77)	.028
Stridor	3.8 (1.4-10)	.008
Dyspnea	2.9 (1.4-5.7)	.003
Hypotension	2.9 (1.3-6.8)	.013
Wheeze	2.2 (1.1-4.6)	.028

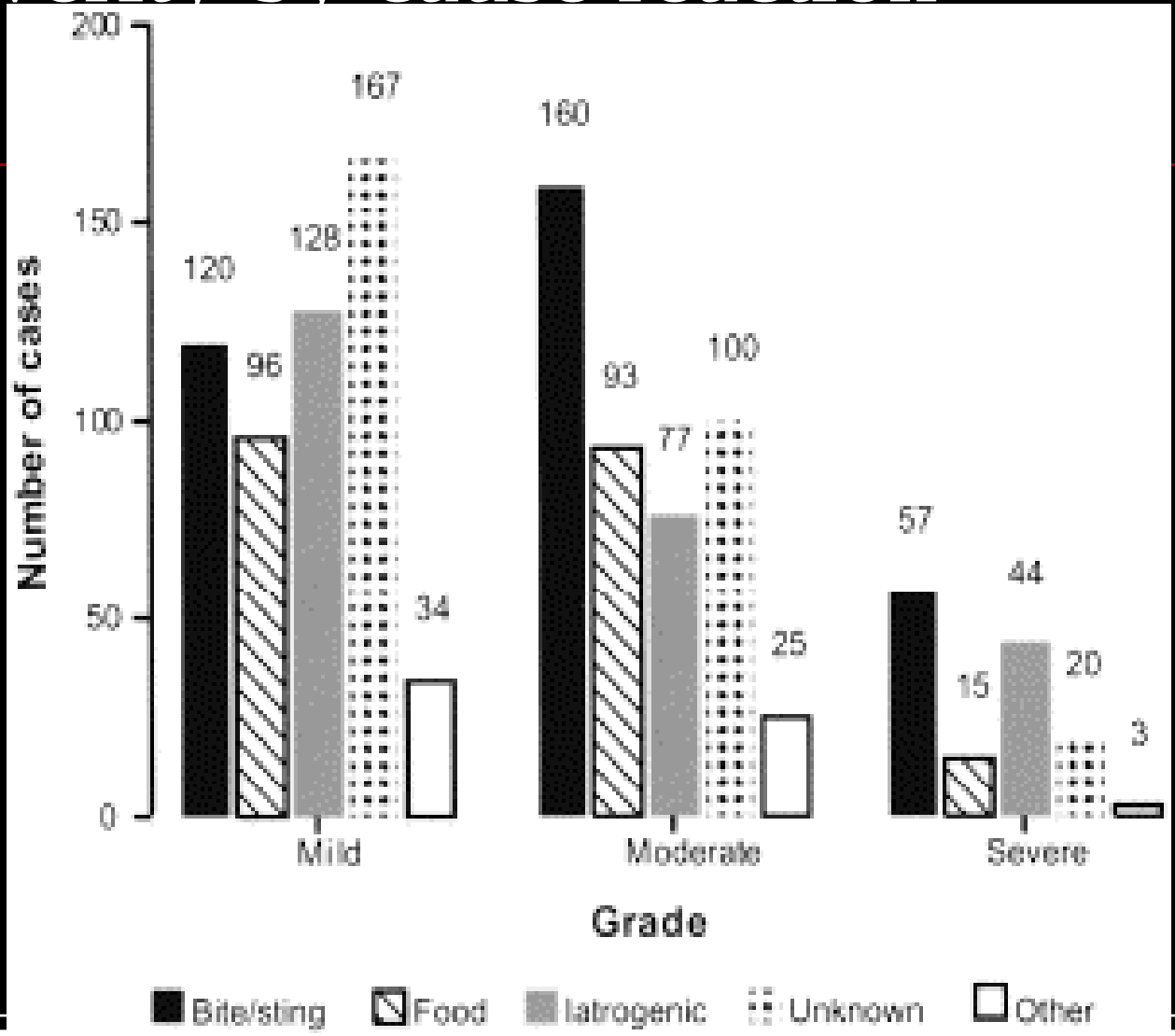
Brown S, JACI, oct 2004

Grading

- Mild (skin and subcutaneous tissues only)
  - Generalized erythema, urticaria, periorbital edema, or angioedema
- Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)
  - Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
- Severe (hypoxia, hypotension, or neurologic compromise)
  - Cyanosis or SpO2 ≤ 92% at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, LOC, or incontinence

Brown S, JACI, oct 2004

Severity by cause reaction



Brown S, JACI, oct 2004

Predictors of severity

- the only independent associations with the severe reaction grade were
  - insect venom (odds ratio 2.7, 95% CI 1.8-4.2),
  - iatrogenic causes (odds ratio 2.3; 95% CI 1.4-3.8)
  - older age (median ages 26, 29, and 44 years for mild, moderate, and severe reactions, respectively; $P < .0001$).

Brown S, JACI, oct 2004

Pediatric experience

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Table 3 -- Differential diagnosis

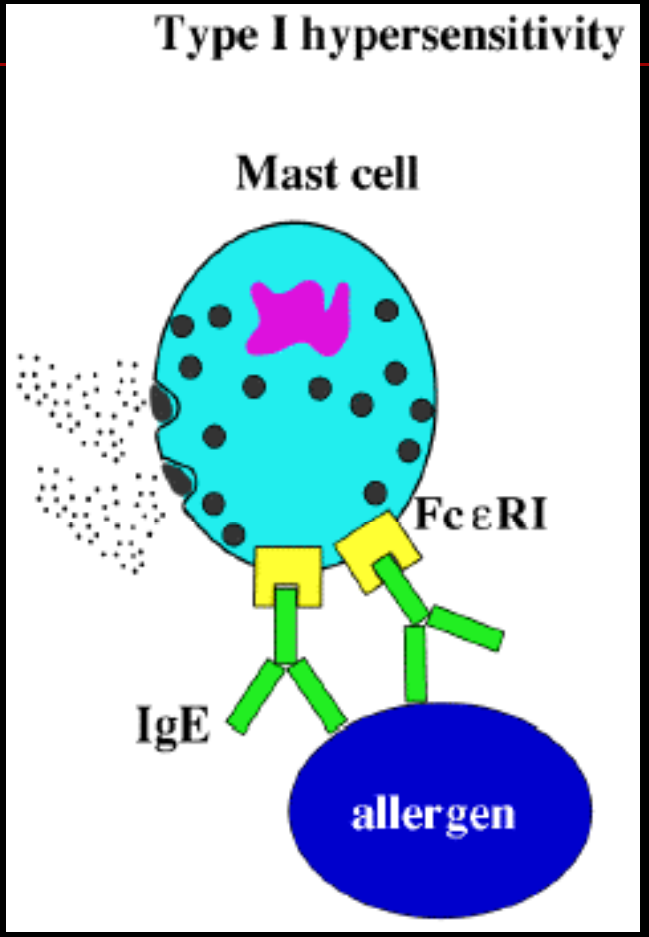
Differential

Hypotension	Vasovagal reaction Hypovolemic/septic shock
Flushing	Carcinoid syndrome Red man syndrome Scromboid fish poisoning Monosodium glutamate ingestion
Urticaria	Urticaria pigmentosa/mastocytosis Scromboid fish poisoning
Respiratory distress (wheezing)	Asthma exacerbation Vocal cord dysfunction Airway foreign body
Angioedema	Hereditary angioedema Serum sickness
Syncope	Vasovagal reaction Pseudoanaphylaxis (procaine penicillin)

Mechanisms

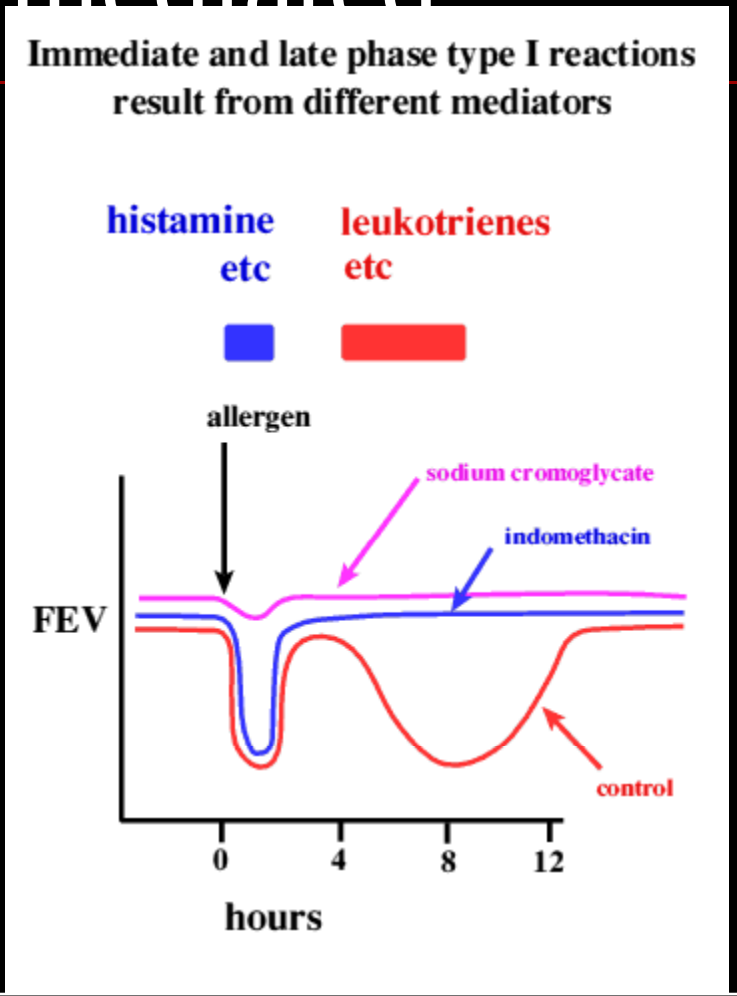
IgE central role

- the aggregation of FcεRI that occurs by the binding of FcεRI-bound IgE to bivalent or multivalent antigen induces the activation of mast cells and basophils



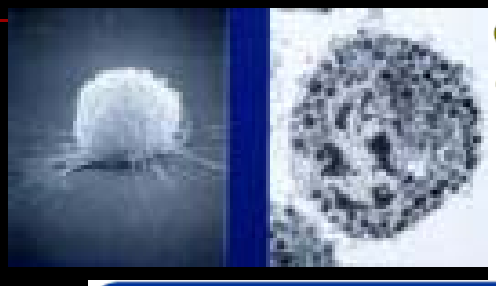
Anaphylaxis is IgE mediated

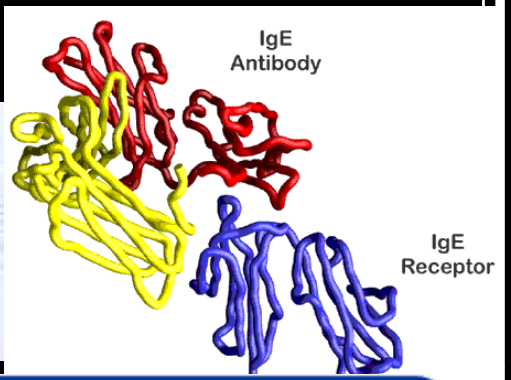
- Results in the rapid and, in the case of cytokines and chemokines, sustained release of diverse mediators that induce anaphylaxis

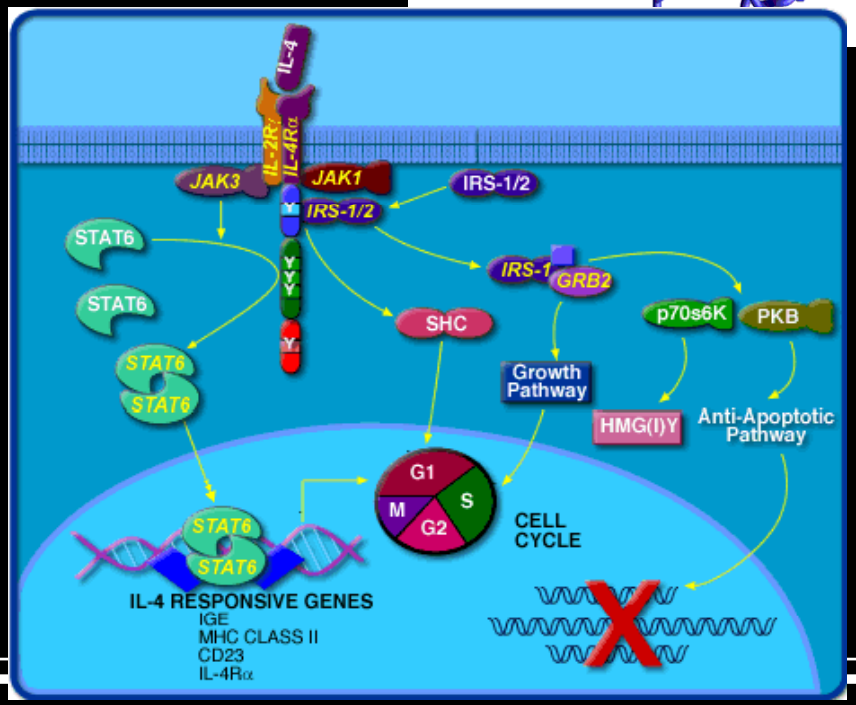


Required elements

- IL-4 and IL-4 receptor
- mast cell
- FcεRI
- IgE
- blocked by histamine receptor 1 antagonists and, to a lesser extent, by PAF antagonists
  (is not inhibited by serotonin receptor or leukotriene antagonists)



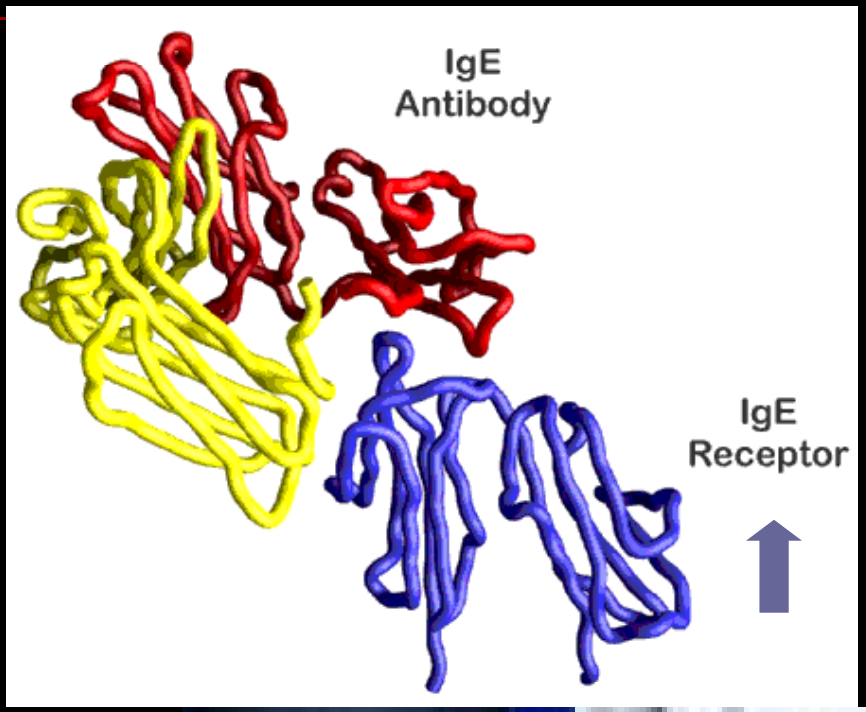


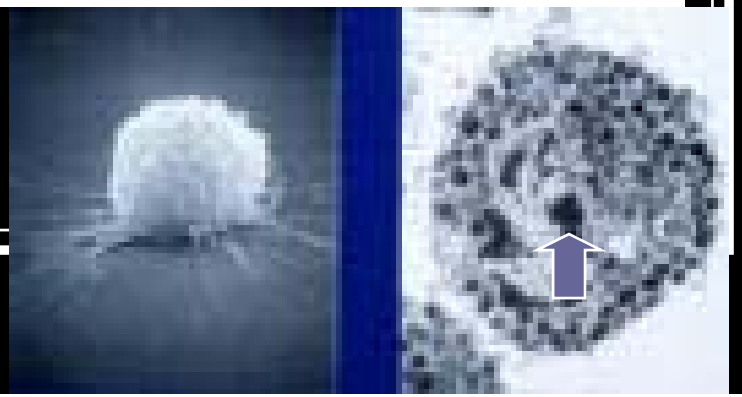


Finkelman FD,JACI 2005

IgE contribute to the intensity of **anaphylaxis**

- IgE sensitizes or primes mast cells and basophils to undergo activation
- Enhance the effector function through increase in surface expression of the FcεRI
  - both in mouse models and in human *in vivo*.
- Enhances mast cell survival and mediator release





Galli S , JACI 2005

Antibody conformation change

- Antibodies can assume at least 2 distinct isomeric conformations in its antigen binding site
  - one of which can bind the known antigen and
  - the other of which can bind, albeit with a lower affinity, a structurally and chemically distinct antigen.

James L.C, Science 2003

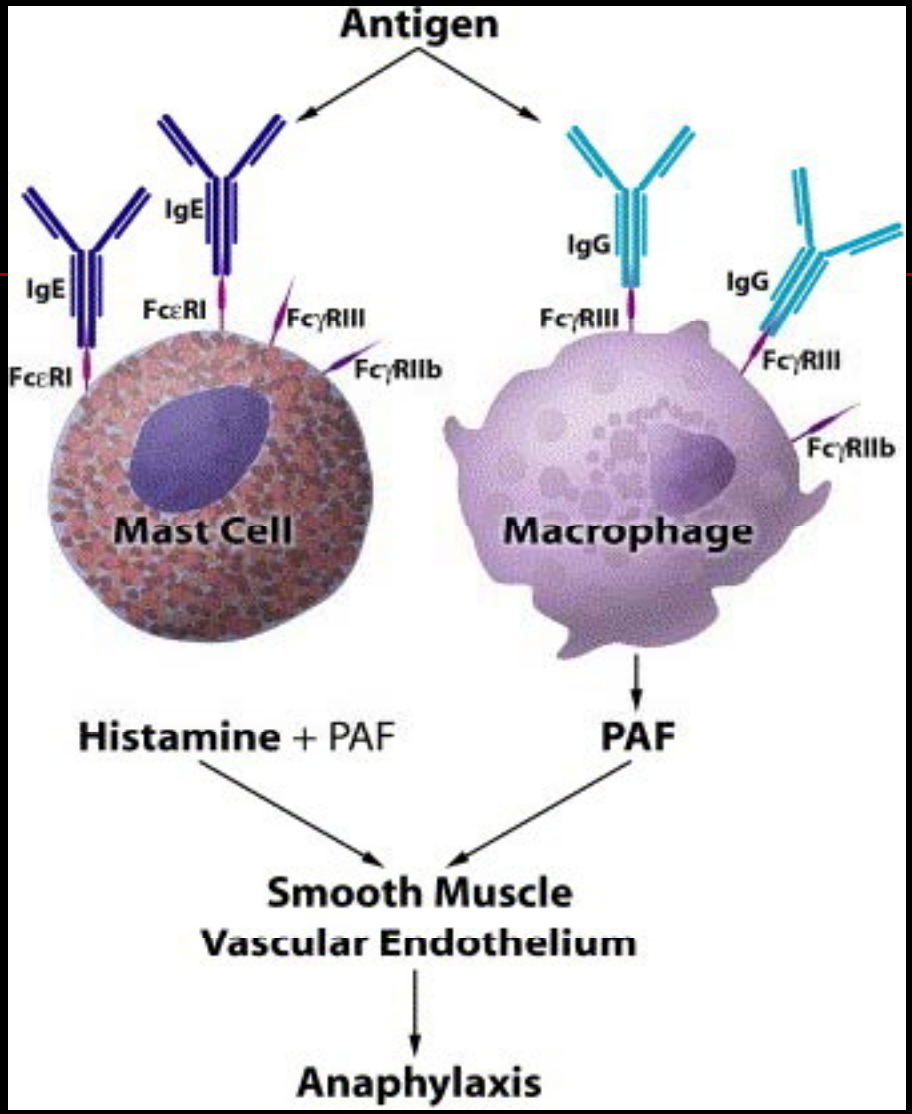
Animal models: what can we learn about them?

Murine model

- Anaphylaxis has classically been defined as a process that is mediated primarily by IgE, FcεRI, mast cells and histamine.
- However, an alternative pathway involving IgG, FcγRIII, macrophages and platelet-activating factor (PAF) may be more important in rodent models of antigen-induced anaphylaxis.

Strait, JACI 2002

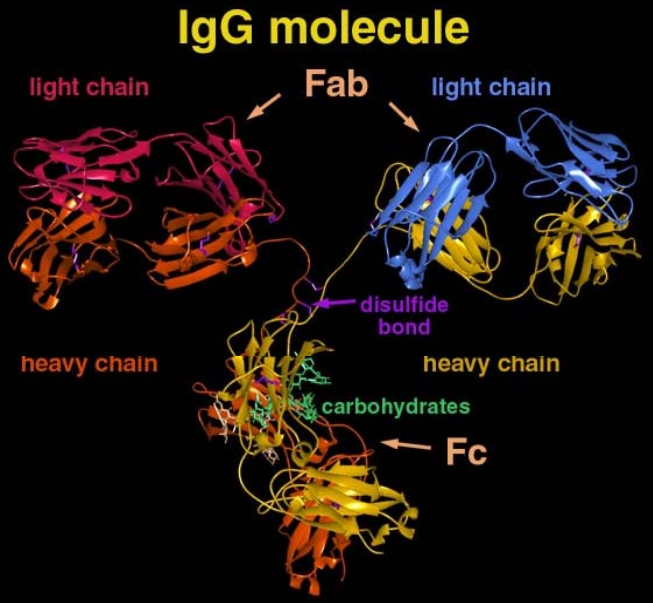
Murine model



Finkelman FD,JACI 2005

IgE independent anaphylaxis

- Required elements
  - IgG antibody
  - macrophages
  - FcγRIII
  - PAF (but not histamine, serotonin, or leukotriene
- Is independent of
  - mast cells, FcεRI, IgE and complement



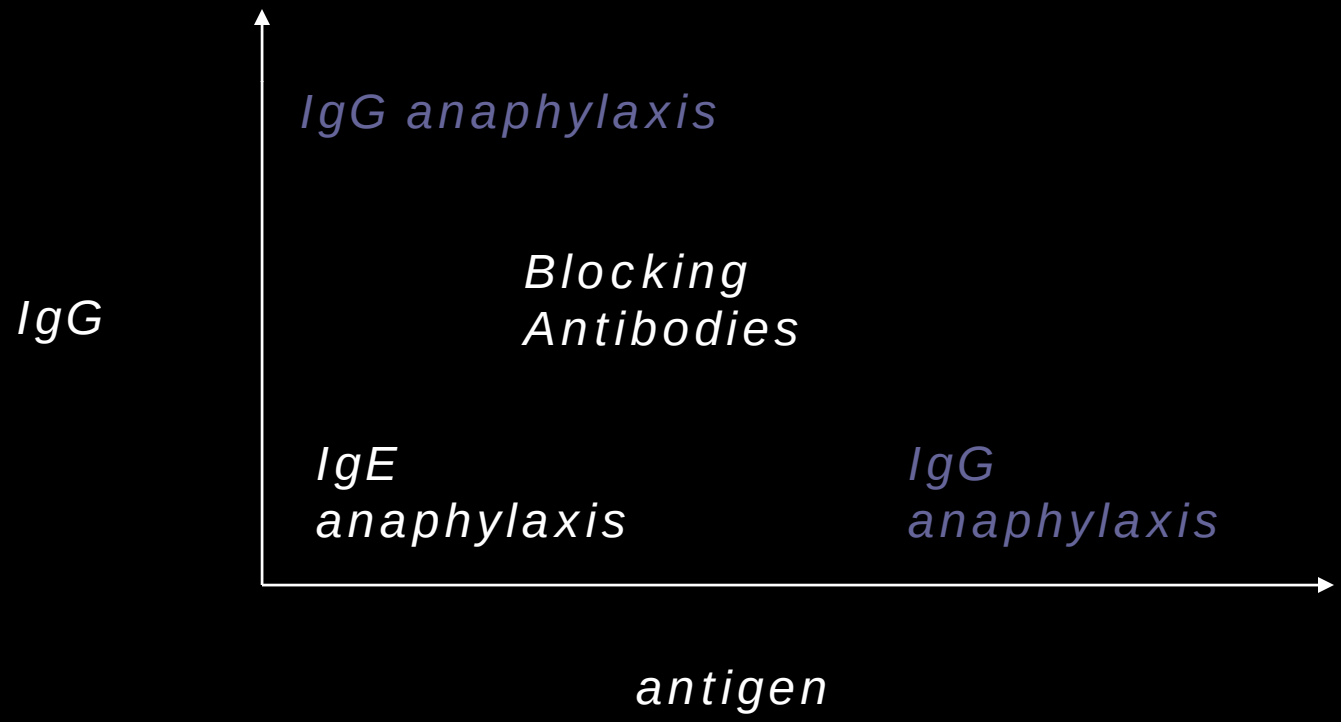
Finkelman FD,JACI 2005

Determinants of IgE-dependent **anaphylaxis**

- quantity of antigen-specific IgG antibody and
- the quantity of antigen used to challenge

Finkelman FD,JACI 2005

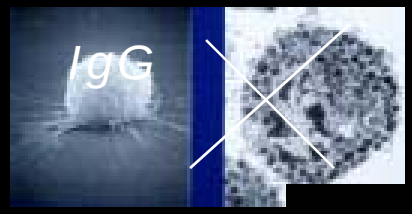
Murine determinants anaphylaxis

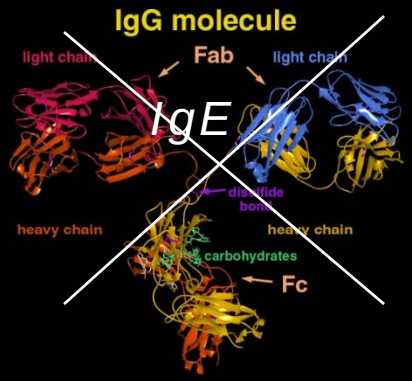


Finkelman FD,JACI 2005

Humans are not mice

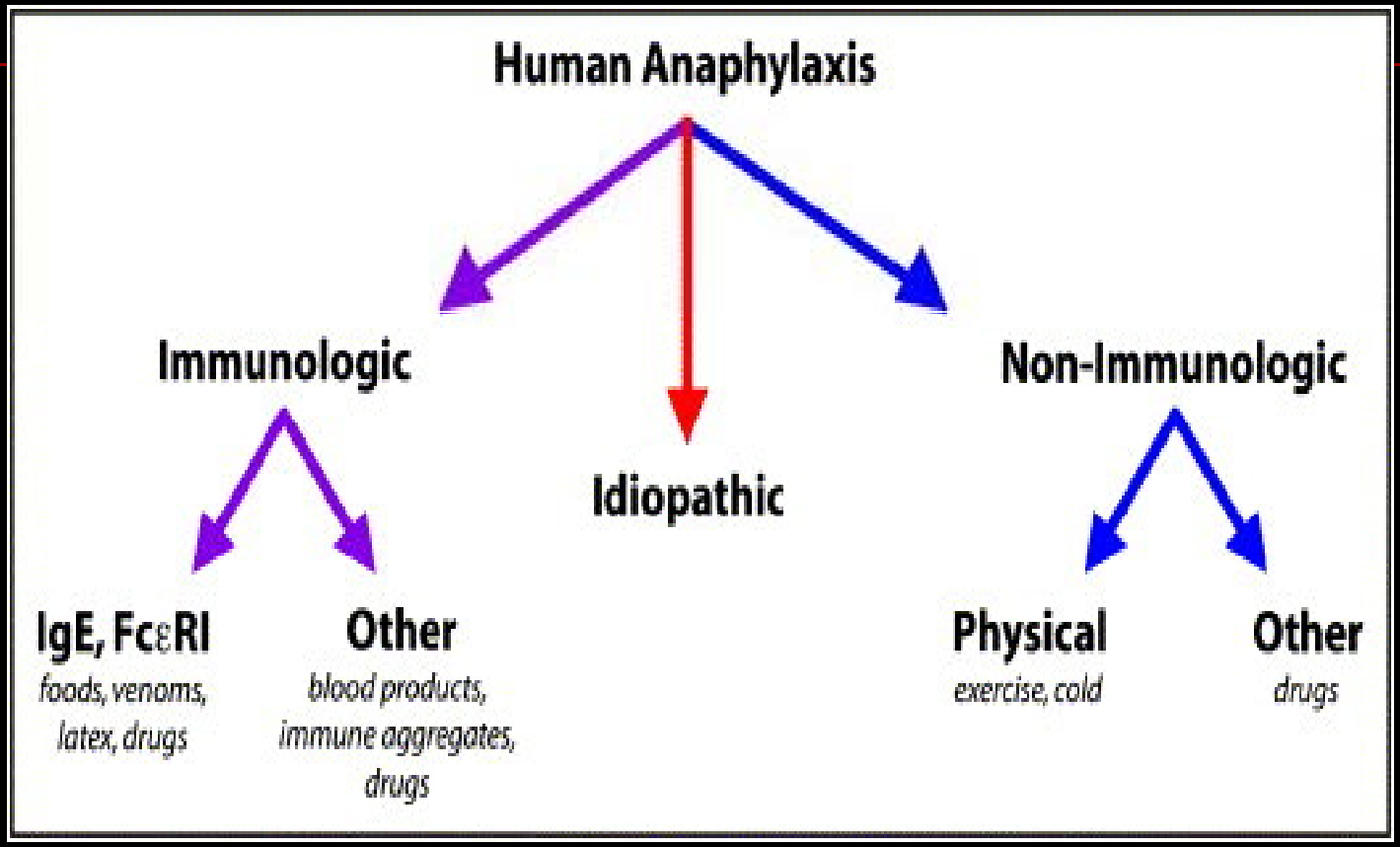
- Human IgG isotype do not activate mast cells
- Human IgE do not bind to low-affinity FcγRs
- Human macrophages, Langerhans, and dendritic cells do express FcεRI
- Human platelets, B cells, natural killer cells, and neutrophils do express low-affinity IgG receptors





Although IgG mediated anaphylaxis has not been described in humans

- Human **anaphylaxis** has been described in which there was no evidence of antigen-specific IgE antibodies or mast cell degranulation products
  - ie, immunoglobulin-independent activation of inflammatory cells
- There are human IgG receptors that can activate macrophages to secrete PAF



Simons E, JACI 2006

Guinea pigs

- Inhalation of reactive low-molecular-weight compounds produced clinical symptoms in the guinea-pig.
- Anaphylactic reactions were obtained only when the molecular weight was approximately 3000 or more.

verdier, Toxicology 1994

Murine model of lung involvement

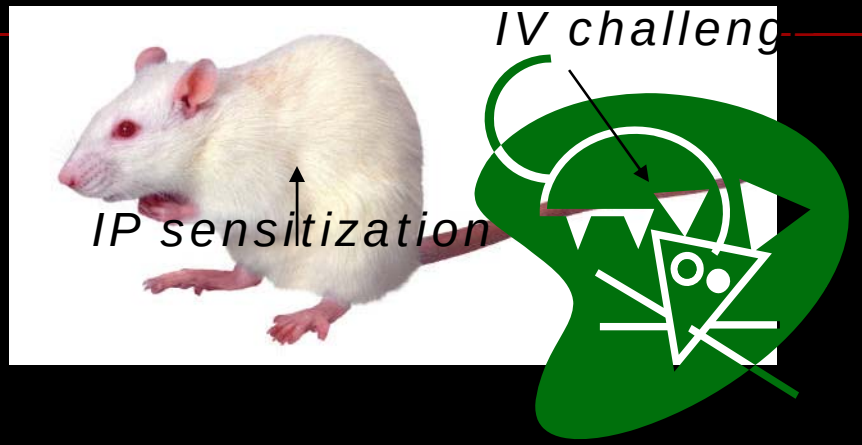
- The development of asthma-like symptoms during **anaphylaxis** appears to require
- pre-existing pulmonary inflammation in addition to systemic mediator release.

Peanut allergy murine model

- Oral inoculation with cholera toxin plus peanut allergens causes
  - diarrhea and
  - systemic symptoms: decreased mobility, wheezing, and hypothermia
- Anaphylaxis is associated with
  - IgE antibody response to peanut
  - low levels IgG to peanut
  - and increased serum histamine levels

Parasite model

- intraperitoneal sensitization and challenge to A. simplex.
- Intravenous A. simplex challenge produced anaphylaxis in mice
- Oral A. simplex challenge did not caused symptoms nor histamine release.
  - Mice experience diarrhea after 5 or more challenges
  - Absent systemic symptoms could be due to blocking antibodies?



Baeza,Clin Exp Immunol. 2005

Mediators

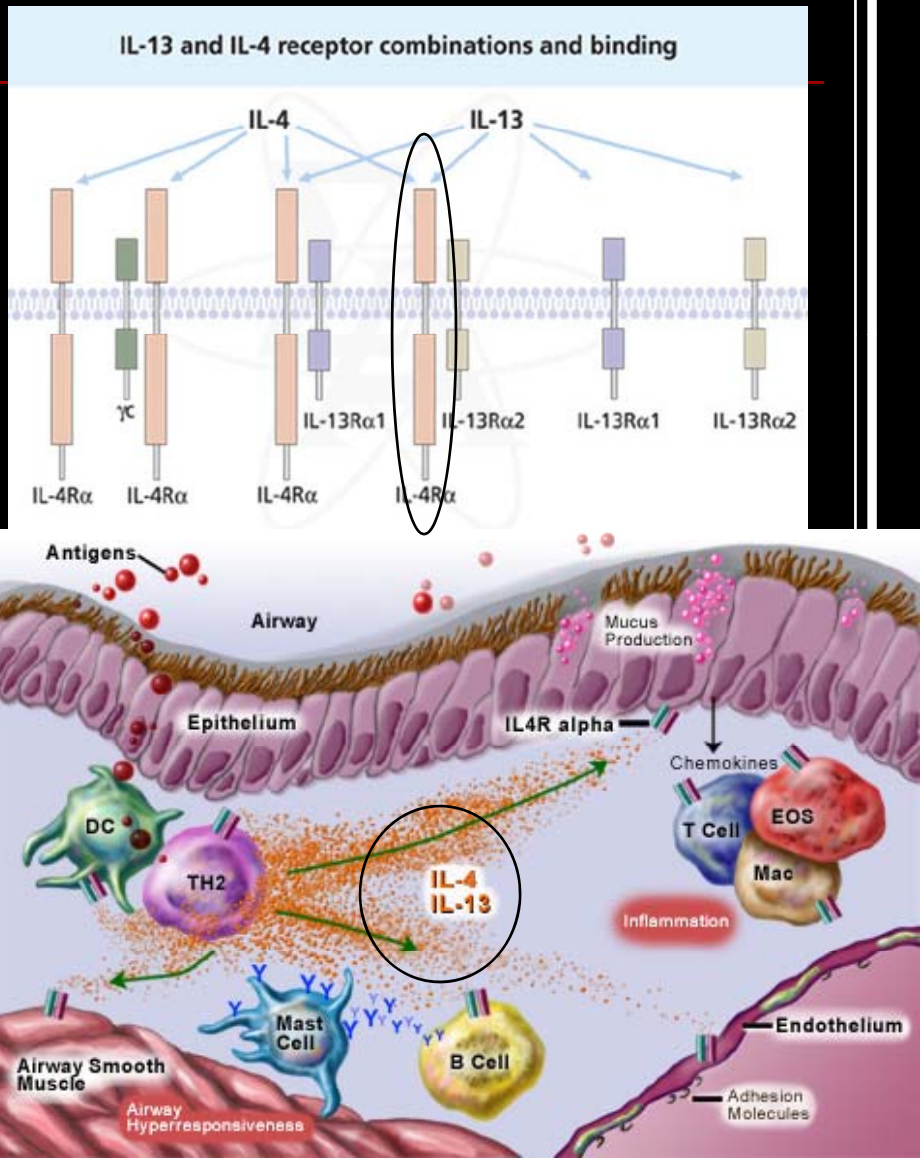
Histamine

- Probably the most important mediator
- Acts through both H1 and H2 receptors
  - The H2 receptors act directly on vascular smooth muscle.
  - H1 receptors act indirectly by stimulating the production of nitric oxide by endothelial cells
- The overall effect is vasodilatation with increased vascular permeability.
  - causes flushing
  - shift in fluid to the extravascular space

Lieberman. Allergy: 2003

Il-4 and Il-13

- generation of the antibody and inflammatory cell responses
- Treatment of mice with IL-4 or IL-13 rapidly and substantially increases the severity of anaphylaxis



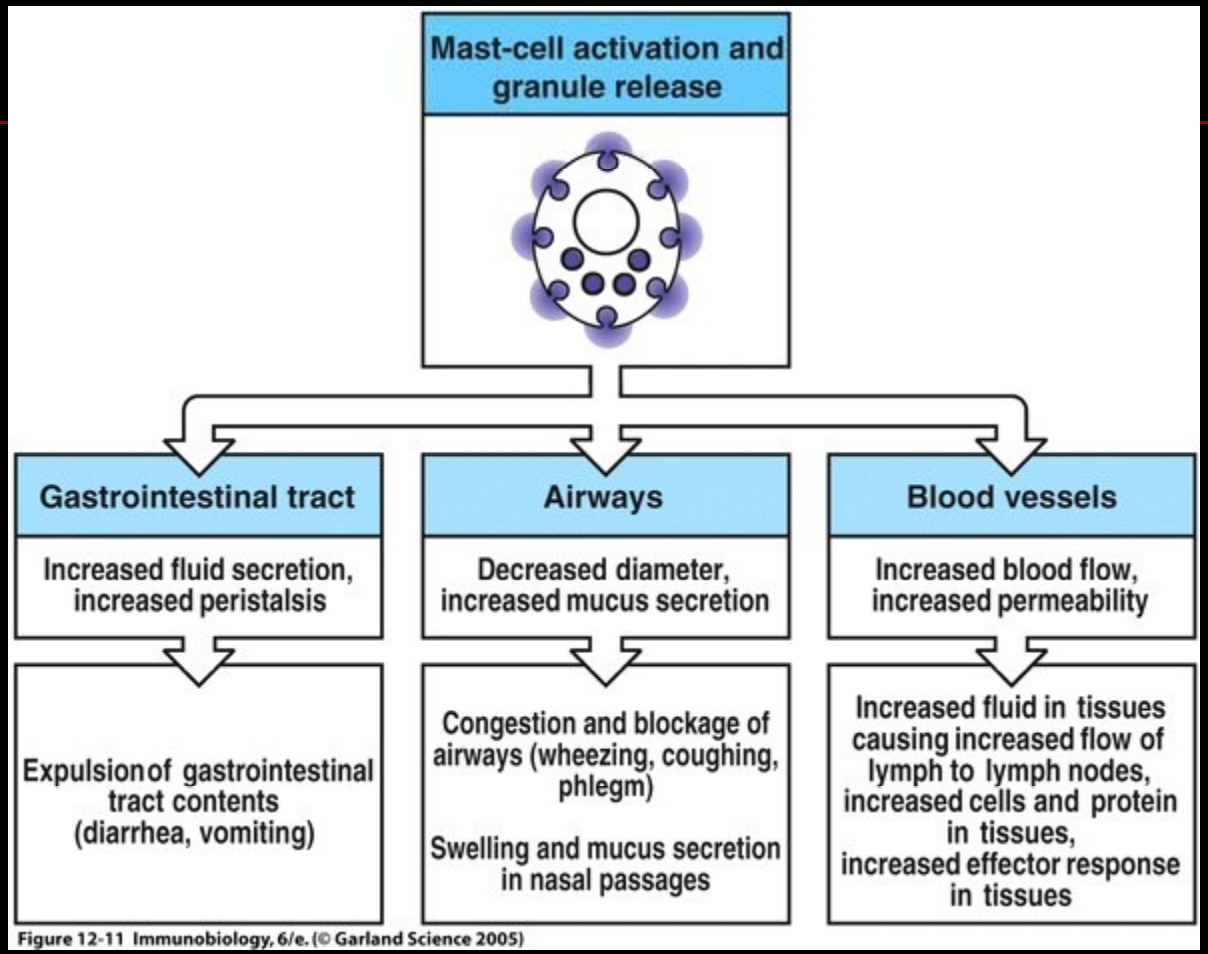
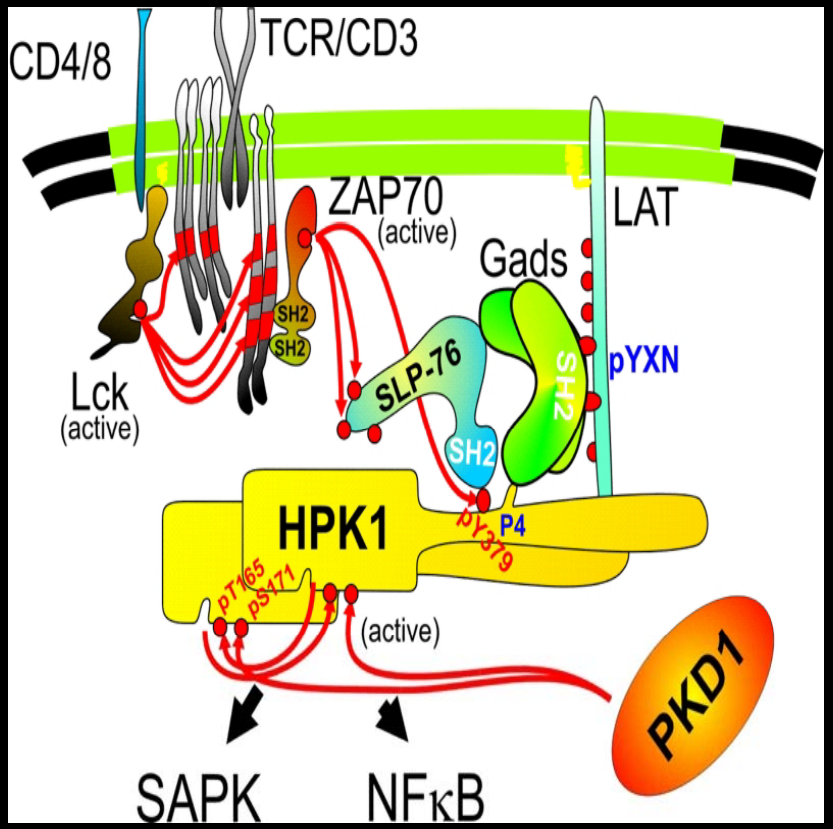


Figure 12-11 Immunobiology, 6/e. (© Garland Science 2005)

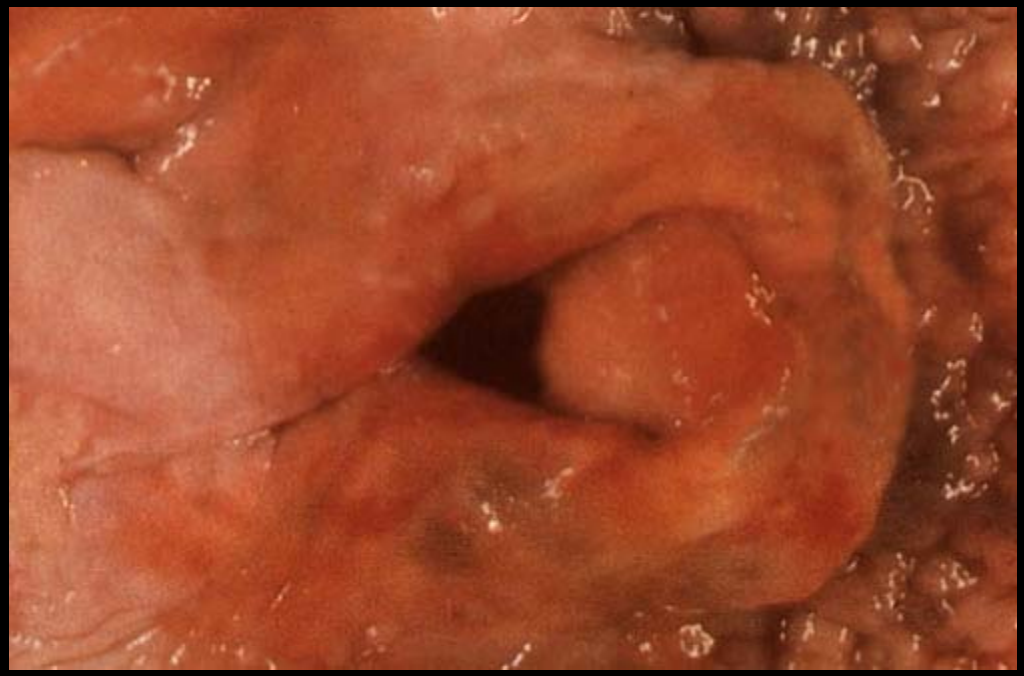
Syk inhibitors



- Mazuc et al reported the discovery of a small molecule that inhibits mast cell degranulation through interruption of Syk signaling

Mazuc et al;JACI 2008

Laryngeal edema



Activation of other inflammatory paths

- In protracted cases of anaphylaxis, one can see activation of the contact system with:
  - the formation of kinins
  - the coagulation pathway (both clotting and clot lysis)
  - and the complement cascade
- Nitric oxide is also produced in large quantities producing vasodilatation and enhancing vascular permeability, worsening shock

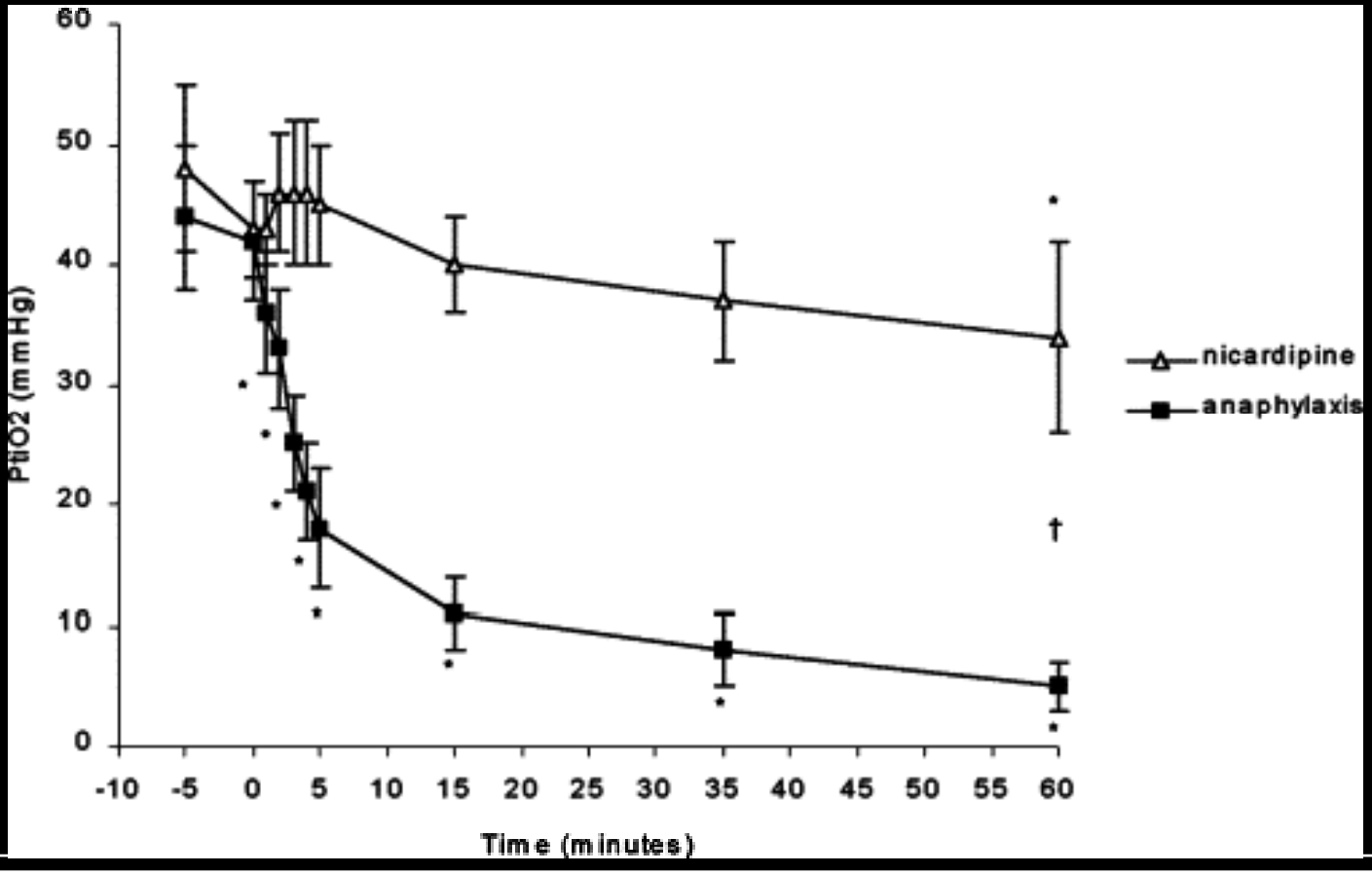
Nicardipine Ova anaphylaxis

- Time course and the magnitude of the hypotension were similar
- Skeletal muscle blood flow decreased in both groups after 20–40 min

- Higher plasma epi and norepinephrine concentrations
- Greater gradient between plasma and interstitial epinephrine
- Rapid decrease in tissue oxygen partial pressure
- Rapid and larger increase in interstitial lactate concentrations, and a decrease in interstitial pyruvate concentrations

Dewachter et al, Anesthesiology 2005

Anaphylaxis produces an immediate and severe decrease in Ptio2



Dewachter et al, Anesthesiology 2005

Anaphylaxis produces a distributive shock

- Preserved cardiac output initially
- Redistribution of blood flow
- Skeletal muscle vasoconstriction related to the activation of SNS
- Anaerobic metabolism related to a rapid decrease in skeletal muscle Ptio2 and increased tissue oxygen consumption
  - increase in lactate/pyruvate ratios, representing a complete failure of energy production within myocytes
- If this phenomenon occurs in other organs, it could result in rapid alteration in their functions and failure of well-conducted resuscitation to restore cardiovascular homeostasis even in previously healthy individuals

Dewachter et al, Anesthesiology 2005

Afterwards…

- While blood pressure declines, pulse increases, cardiac output declines, and intravascular volume diminishes as shock progresses
- Peripheral vascular resistance may in some cases paradoxically increase.
  - This increase is caused by endogenous compensatory responses (epinephrine, angiotensin II, endothelin) -all of which are vasoconstrictive, or
  - exogenous vasoconstrictors (epinephrine, dopamine)
- Patients that do not respond to the administration of vasoconstrictor agents require large volumes of fluid for resuscitation.

- Fluid extravasation causing hemoconcentration, hypovolemia
- and reduced venous return to the heart manifested as low
- filling pressures and reduction in cardiac output

- Venodilation and blood pooling, contributing to reduced venous return
- Impaired myocardial contractility contributing, along with reduced venous return, to reduced in cardiac output
- Relative bradycardia (neurally mediated) in awake patients, contributing to reduced cardiac output
- Early transient increase in pulmonary vascular resistance,contributing to the

Anaphylaxis

When Seconds Count . . .

Be prompt!

- Anaphylactic reactions are often life-threatening and almost always unanticipated.
- Even when there are mild symptoms initially, the potential for progression to a severe and even irreversible outcome must be recognized.
- Any delay in the recognition of the initial signs and symptoms of **anaphylaxis** can result in a fatal outcome either because of airway obstruction or vascular collapse.

epinephrine

- Incremental doses of epinephrine lead first to stimulation of β2 receptors followed by β1 and α-adrenergic receptors.
  - cardiac function was preserved in the early stages of **anaphylaxis**.
  - β2-Receptor effects lead to bronchodilation and the increased production of cyclic AMP.

- timely diagnosis and management are essential to prevent rapid cell and organ dysfunction

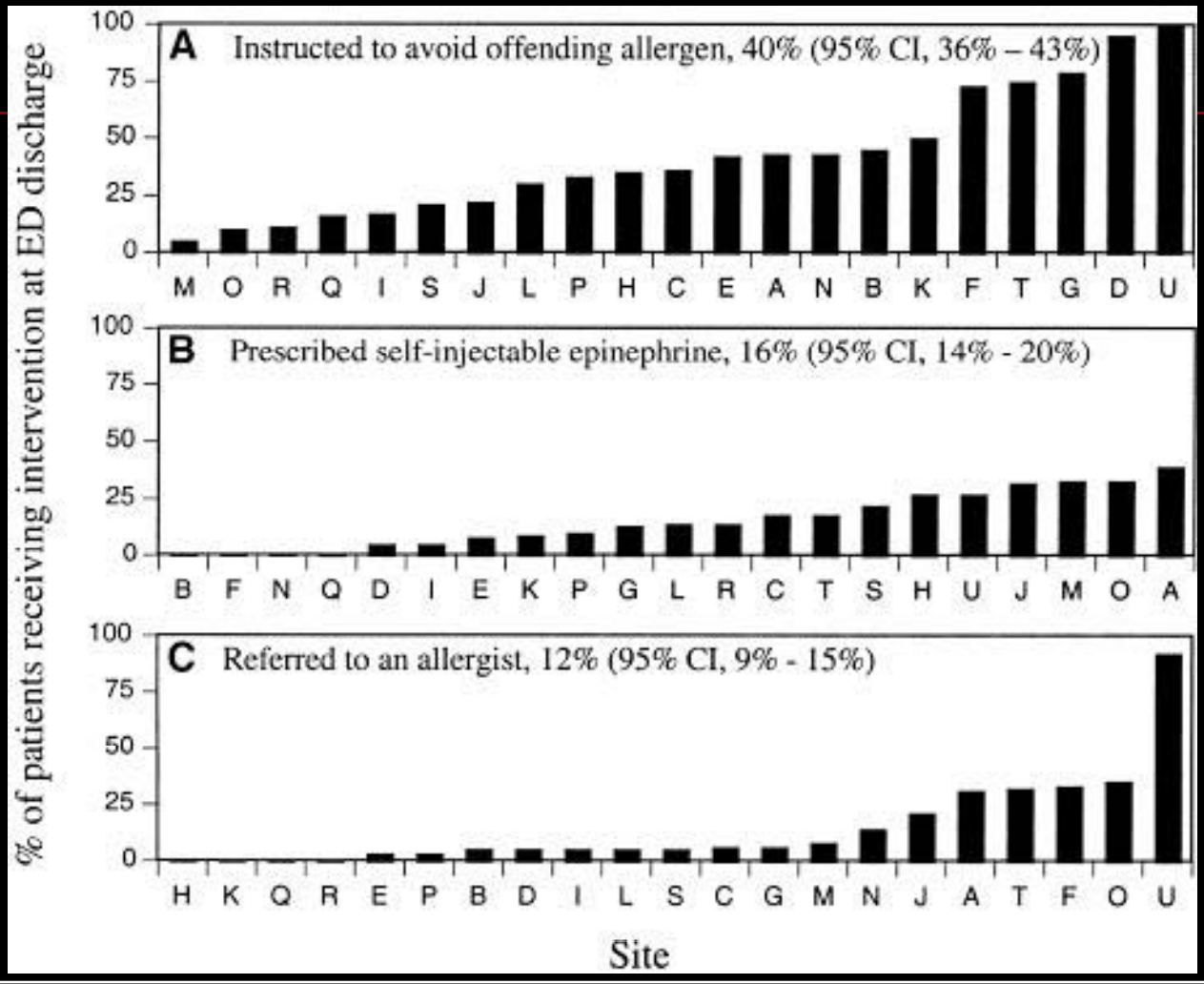
How are we doing?

Treatment of food anaphylaxis

- Randomly selected cohort of 678 from the 5296 charts with a physician diagnosis of an acute allergic reaction to food
- Crustaceans, peanuts, and fruits and vegetables were the most common causes
- Less than 20% of patients were brought to the ED by ambulance.
- Approximately one third of patients sought medical attention within 1 hour of symptom onset, 72% within 3 hours, and 81% within 6 hours. (median was 2 hours)
- Within 3 hours of ED arrival, 11% (95% CI, 8% to 13%) of patients had documentation of use of intramuscular or subcutaneous epinephrine.

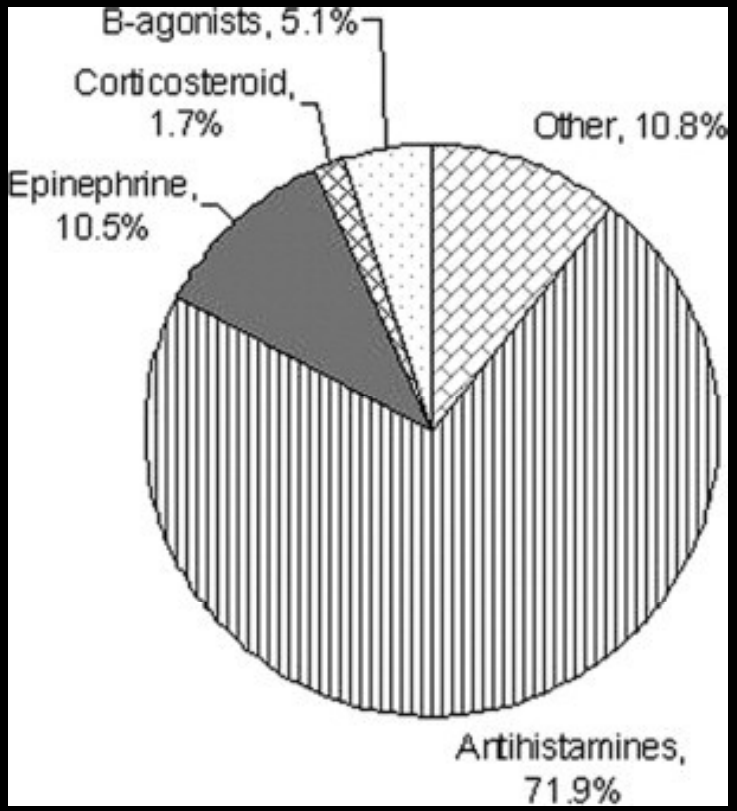
Clark S. JACI 2004

ER treatment



Clark S. JACI 2004

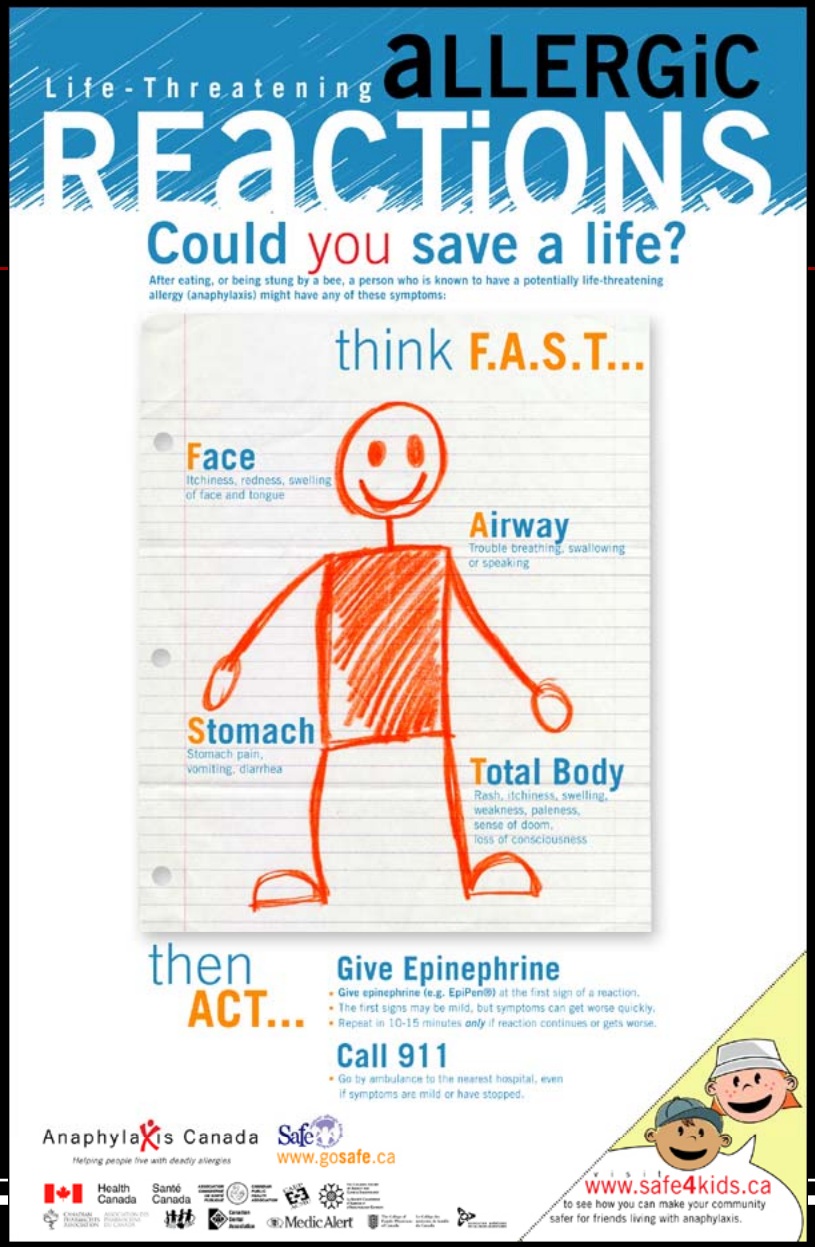
Tx of anaphylaxis prior to arrival to ED



Anaphylaxis prevention

Sabrina's law

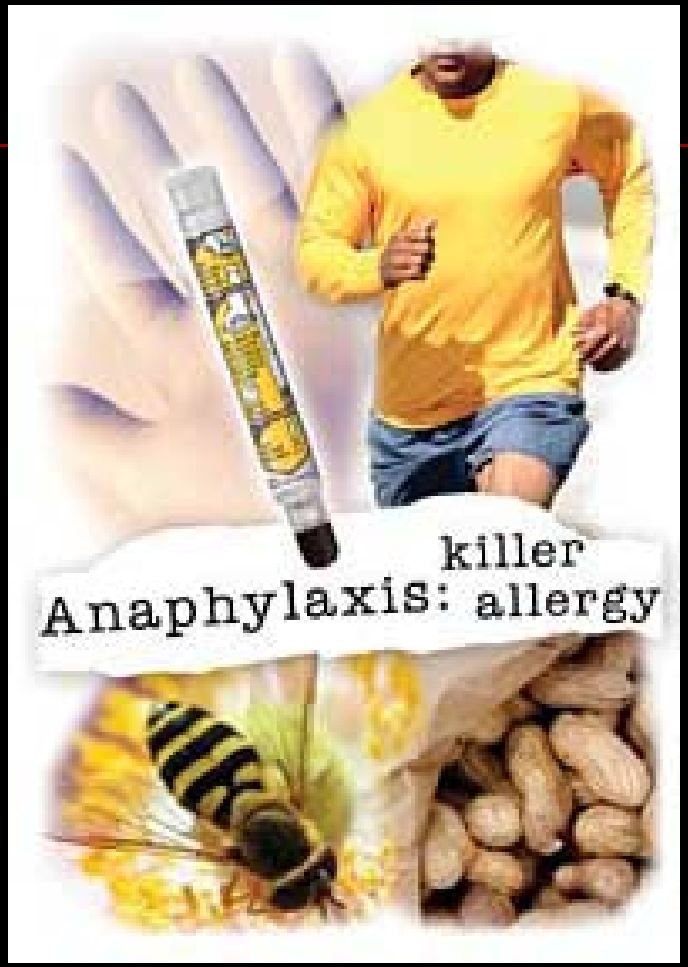
- On January 1, 2006, it became law for all school boards in Ontario to have standards in place to protect children at risk for anaphylaxis.
- Requires schools to:
  - reduce the risks of causative allergens
  - identify children with life-threatening allergies
  - establish emergency measures to treat a reaction
  - provide regular staff training in the use of epinephrine
  - ensure school-wide communication of the standards.


Life-Threatening ALLERGIC REACTIONS
Could you save a life?
After eating, or being stung by a bee, a person who is known to have a potentially life-threatening allergy (anaphylaxis) might have any of these symptoms:
think F.A.S.T...
Face
Itchiness, redness, swelling of face and tongue
Airway
Trouble breathing, swallowing or speaking
Stomach
Stomach pain, vomiting, diarrhea
Total Body
Rash, itchiness, swelling, weakness, paleness, sense of doom, loss of consciousness
then ACT...
Give Epinephrine
Give epinephrine (e.g. EpiPen®) at the first sign of a reaction.
The first signs may be mild, but symptoms can get worse quickly.
Repeat in 10-15 minutes only if reaction continues or gets worse.
Call 911
Go by ambulance to the nearest hospital, even if symptoms are mild or have stopped.
Anaphylaxis Canada
Helping people live with deadly allergies
Safe
www.gosafe.ca
Health Canada
Santé Canada
MedicAlert
visit www.safe4kids.ca to see how you can make your community safer for friends living with anaphylaxis.

When to refer to an allergist?

- Anaphylaxis without an obvious trigger
- Food anaphylaxis
- Exercise induced anaphylaxis
- Drug induced anaphylaxis

Amercan Academy Allergy, Asthma & Immunology, JACI 2006;S495-521



Asociación Puertorriqueña de Médicos Alergistas

Allergy Immunology Fellowship

AI Fellowship RCM

- ACGME approved 2009
- 2 years
- Subspecialty of IM or Pediatrics
- Accepting applications for July 2009

AI fellowship

- Rotations
  - UDH: inpatient AI consult and outpatient clinics for Rheuma, Derma, Ent, Hematology, Lab medicine, Aerobiology
  - San Lucas Ponce: Inpatient pediatrics (3 Months)
  - UPH: Inpatient consults, one month rotation Pediatric AIDS
  - Auxilio: Transplant (one month)
  - VA: Outpatient Adult AIDS (one month), Pulmo lab (one month)
  - UPR Hospital at Carolina- outpatient Ophta (one month), ER (one month)

AI fellowship

- Academic experiences
  - JC
  - Research in progress: Faculty, fellows and Invited attending
  - Chapter review
  - Core Allergy and Immunology Lectures

AI fellowship

- Research
  - Conduction of a project
  - Currently working on:
    - Molds and asthma- B Bolaños
    - Bronchiolitis and asthma- Dr Lube
    - Chronic urticaria- Dr. Tirado
    - Allergen prevalence in PR- APMA
    - Asthma Control test validation in PR-APMA
    - B agonist polymorphism in asthma in ER- Dr. Mercado

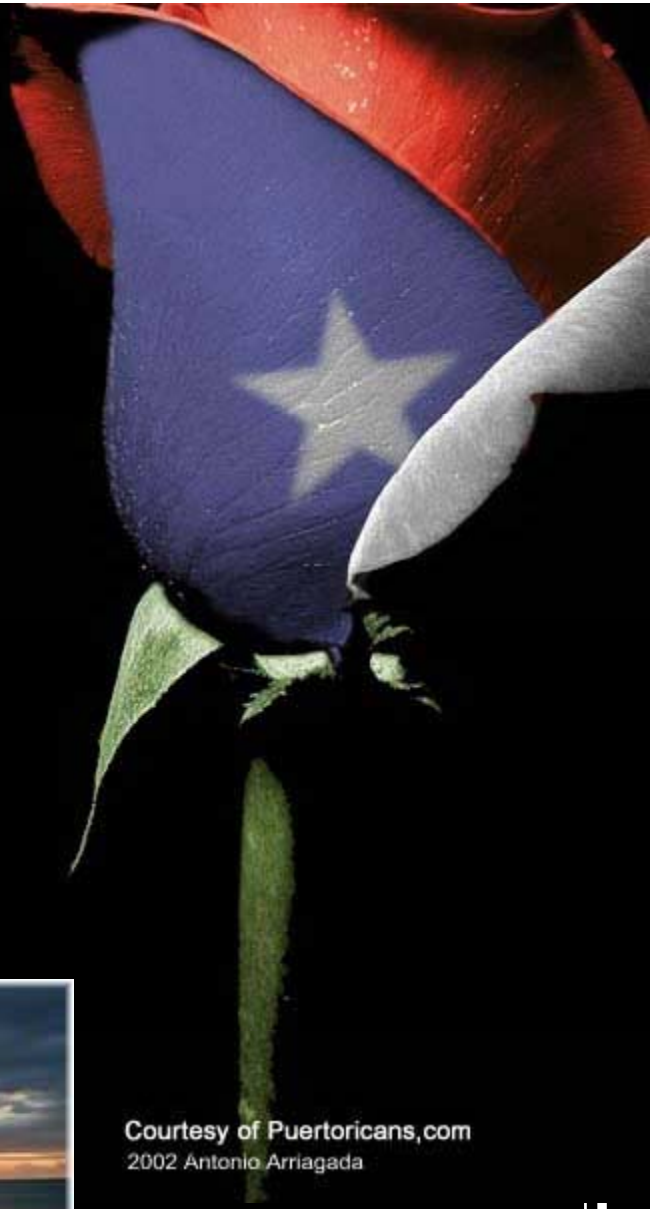
La Boriqueña

La tierra de Borinquén
donde he nacido yo,
es un jardín florido
de mágico fulgor.
Un cielo siempre nítido
le sirve de dosel
y dan arrullos plácidos
las olas a sus pies.

Cuando a sus playas llegó Colón;
Exclamó lleno de admiración;
"Oh!, oh!, oh!, esta es la linda
tierra que busco yo".

Es Borinquén la hija,
la hija del mar y el sol,
del mar y el sol,
del mar y el sol,
del mar y el sol,
del mar y el sol.

Manuel Fernández Juncos (1846-1928)



Anaphylaxis in PR

- What is the prevalence and mortality?
- Could we expect higher severity and prevalence based on high atopy rates?
- Could pulmonary involvement be more significant?
- How many anaphylaxis are not IgE dependent?

- However, in both human and mice, similar clinical events can be induced by mechanisms that involve other pathogenetic pathways.
  - in mouse models at least, such mechanisms can account for antigen-dependent **anaphylaxis** in the virtual absence of tissue mast cells or IgE.

Antigen modification

- Hypothesized that slowing the rate of absorption of medication might decrease the rate of anaphylaxis to the insulin peptide B:9-23 in a non obese mice

Liu E, JACI 2004

Table II. Anaphylaxis induction in sensitized NOD mice by using B:9-23 compared with B:9-23RR, B:9-23RR given at pH 3, and B:9-23RRRR

	B:9-23, 100 µg/dose, pH 7	B:9-23RR, 100 µg/dose, pH 7	B:9-23RR, 100 µg/dose, pH 3	B:9-23RRRR, 100 µg/dose, pH 7
#anaph.	67/69	2/45	17/22	11/12
%	97%	4%	77%	92%

Liu E, JACI 2004

Implication for vaccine preparation

- peptide vaccine modification resulting in a decreased solubility when administered subcutaneously, decrease risk of anaphylaxis

Liu E, JACI 2004

Future

- Is IgG dependent anaphylaxis possible and relevant in humans?
- How is the best way to induce antigen specific blocking IgG and IgA without increasing IgE?
- What is the role of blocking Il-4 and/or Il-13 in anaphylaxis?