Anaphylaxis Practice Parameter Update 2015

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Disclosures of Potential Conflicts of Interest

Speakers Bureau:
Genentech/Novartis

Clinical Trials (research contracts):
Genentech/Novartis

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Greer/Stallergenes

The diagnosis and management of anaphylaxis practice parameter: 2015 Update.

(Lieberman et al. Ann Allergy Asthma Immunol 2015;115:341-384.)

4 new sections:

1. A discussion on the definition of anaphylaxis
2. Anaphylaxis in mastocytosis and monoclonal mast cell activating syndrome (MCAS)
3. Unusual presentations of anaphylaxis
4. Controversies and Unsettled Issues:
   - Prescription of epi
   - SCIT
   - LLR to stings
   - OAS
   - facial contact urticaria
   - skin or GI reaction
   - elderly cardiac patient

Anaphylaxis: Diagnostic Criteria

(Sampson et al: JACI 2006;117:391-7)

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

1. Acute onset reaction with skin/mucosal signs **AND**
   – Respiratory compromise and/or reduced BP
2. Rapid onset, after exposure to a ***likely*** allergen for that patient, of 2 or more of:
   - Skin/mucosal signs
   - Respiratory compromise
   - Reduced BP
   - Persistent GI symptoms
3. Reduced BP (>30% drop) after exposure to a ***known*** allergen for that patient

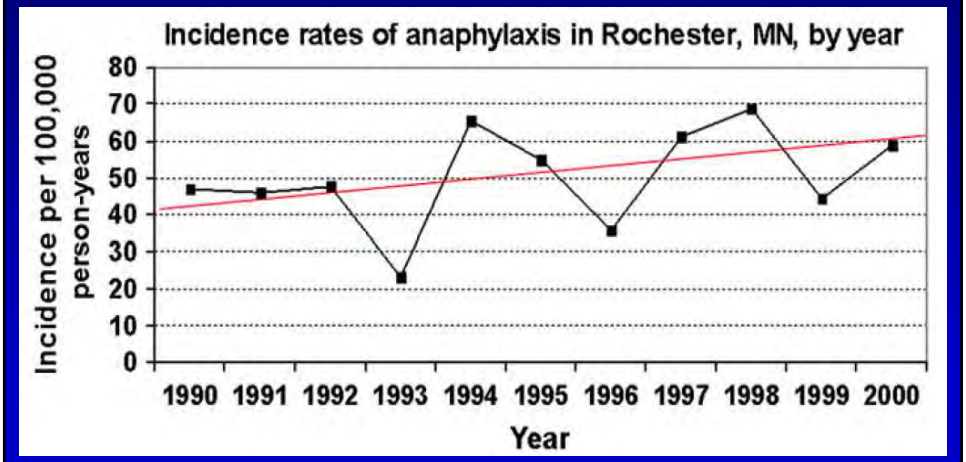
Grading System for Generalized Allergic Reactions (SGA Brown; JACI 2004;114:371)

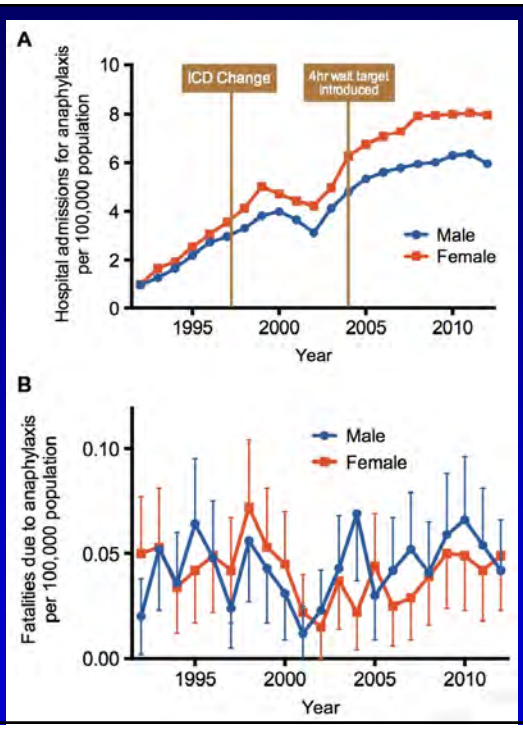
Grade	Defined by
1 – Mild (skin and subcutaneous only)	Generalized erythema, urticaria, periorbital edema or angioedema
2 – Moderate (respiratory, cardiovascular or GI)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest/throat tightness, or abdominal pain
3 – Severe (hypotension, hypoxia, or neurologic compromise)	Cyanosis, SpO2 ≤92%, hypotension, (SBP<90 in adults), confusion, LOC, or incontinence

Epidemiology of Anaphylaxis

Incidence of anaphylaxis in Rochester Minnesota

(Decker WW et al. J Allergy Clin Immunol 2008; 122:1161-5.)

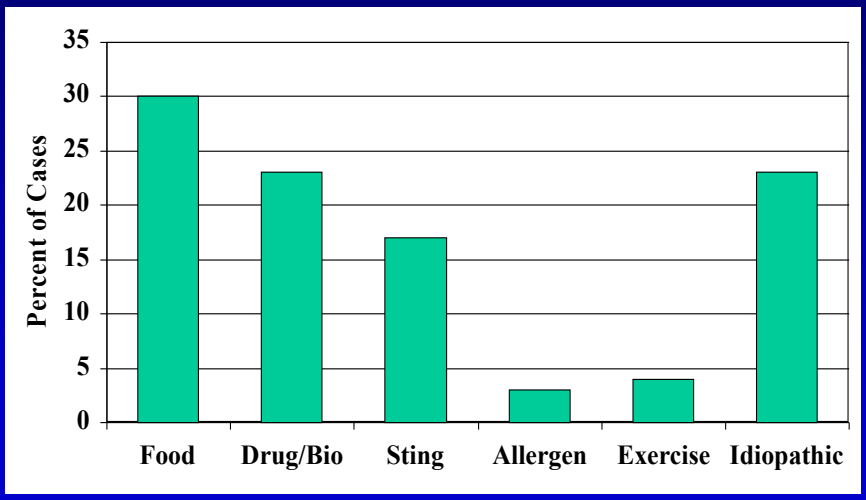




Anaphylaxis hospitalization and fatality rates in the UK 1992-2012

Turner et al JACI 2015; 135:956-963

Causes of Anaphylaxis



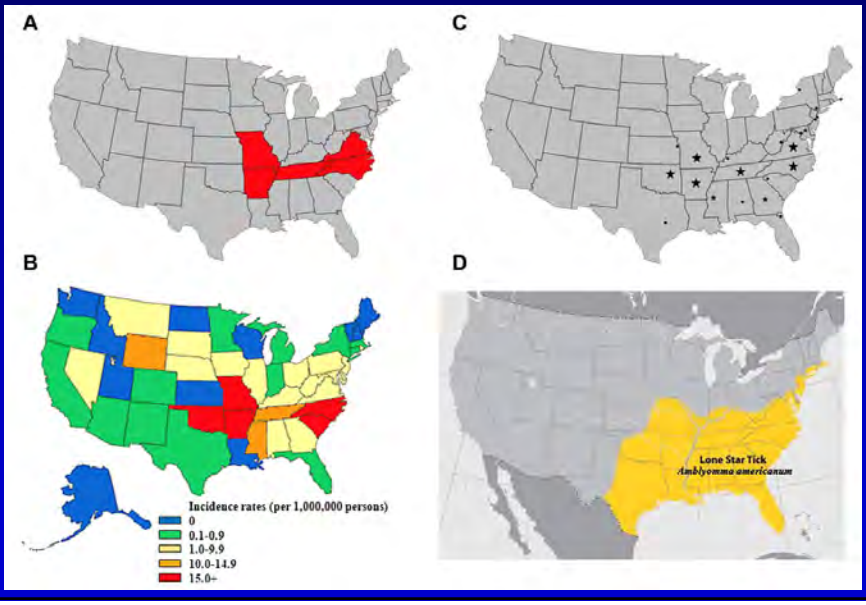
Idiopathic Anaphylaxis

- Mast cell/basophil defect (activation disorders)
  - Receptor mutation (clonal mast cell disorder)
    - KIT (stem cell factor) (mastocytosis)
    - FcERI (IgE)
  - Signaling pathways
    - specific kinases (Syk), phosphatases (SHIP)
    - Non-clonal ("releasability")
- Mediator activity (histamine deaminase, PAF hydrolase)
- Unrecognized allergen (food, NSAID, exercise)

Alpha – Gal Anaphylaxis

Distribution of alpha gal sensitization

(Commins et al, JACI 2011;127:1286-93.)

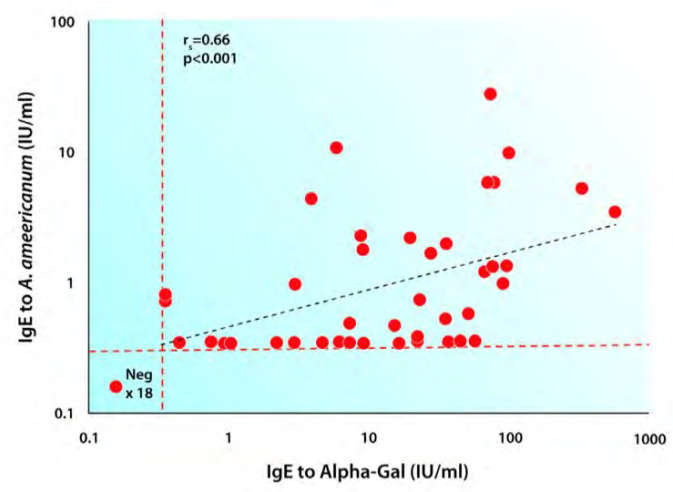


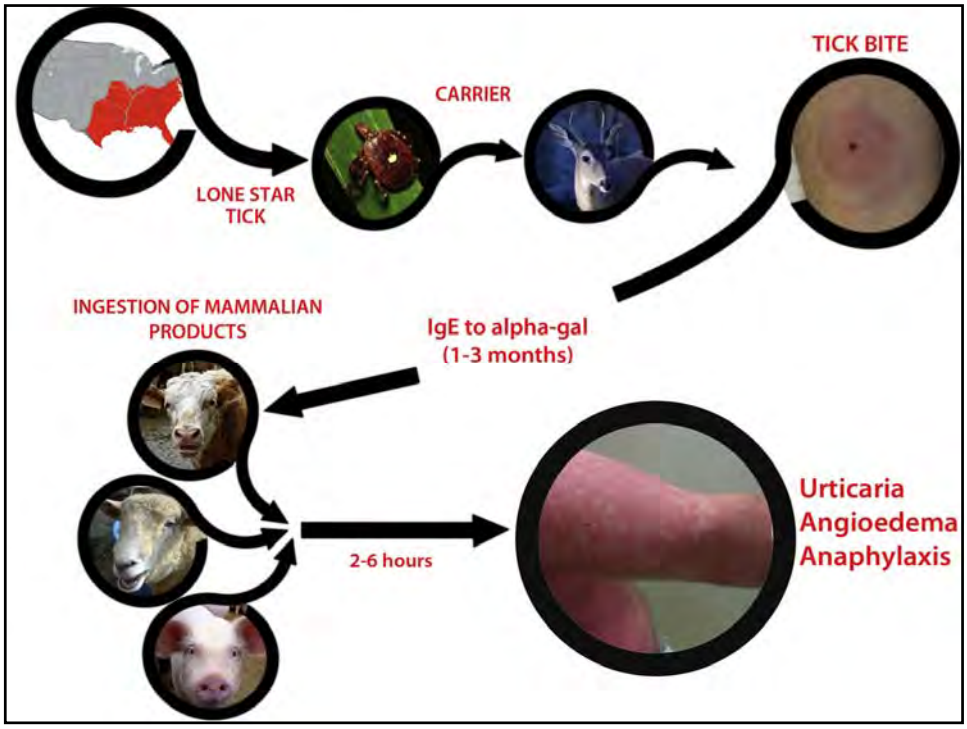
Year: Events leading to our understanding of red meat allergy
~2000: At least 2 groups reported cases of meat allergy that started after tick bites.
2003: IgE to cat allergens is common in an African village but not related to symptoms.
2005: There are reports of hypersensitivity reactions to first infusion of cetuximab in clinical trials.
2007: Severe reactions to cetuximab are common in Tennessee, North Carolina, Arkansas, Missouri, and Virginia.
2007: Two cases in Virginia of adult-onset delayed anaphylaxis occurring 3 to 6 hours after eating beef are reported.
2008: Alpha-gal is identified as the epitope on cetuximab.
2009: Twenty-four cases of delayed anaphylaxis to red meat are found in the United States.
Multiple cases of meat allergy after tick bites are reported in Sydney, Australia.
2010: There is a range of evidence that ticks are responsible for the IgE response in the United States.
2011: There is extensive evidence that the IgE response is not related to asthma, despite cross-reactions with dog and cat.
2014: Open challenge tests confirm the delay in reactions to red meat.

Steinke, Platts-Mills, Commins. JACI 135:589-96

Alpha-Gal IgE Correlates with Tick IgE

(Steinke, Platts-Mills, Commins. JACI 135:589-96)





Alpha- Gal content of various food products

(Mullins et al, JACI 2012)

Beef thyroglobulin	5.6 mcg per gram
Cetuximab	10.2 mcg per 5 mg
Milk / Dairy products	
heavy cream	1.4 mcg per gram
milk (skim, 1%, 2%)	none detected
Gelatin	?

Mast Cell Activation Disorders

Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol. 2010;126:1099.

Global classification of mast cell activation diseases[7]

Classification	Diseases
Primary	Mastocytosis (systemic or cutaneous)
	Monoclonal mast cell activation syndrome
Secondary	Allergic diseases
	Mast cell activation–associated chronic inflammatory or neoplastic disorders
	Physical urticarias
	Chronic autoimmune urticaria
Idiopathic	Mast cell activation syndrome
	Idiopathic anaphylaxis
	Idiopathic urticaria
	Idiopathic angioedema (with or without urticaria)

World Health Organization criteria for systemic mastocytosis[a,3]

Criterion	Description
Major	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in biopsy specimens of bone marrow and/or extracutaneous organs
Minor	1. Abnormal morphologic findings in >25% of mast cells in bone marrow or extracutaneous organs via smear or histologic analysis 2. Expression of CD2 and/or CD25 on mast cells 3. c-kit mutation at codon 816 in lesional tissue 4. Serum total tryptase >20 ng/m: (not valid if there is an associated hematologic disorder)

[a]Diagnosis of systemic mastocytosis can be made if major criterion and at least 1 minor criterion or at least 3 minor criteria are fulfilled.

Lee MJ, Akin C. Mast cell activation syndromes.
Ann Allergy Asthma Allergy 2013;111:5-8.

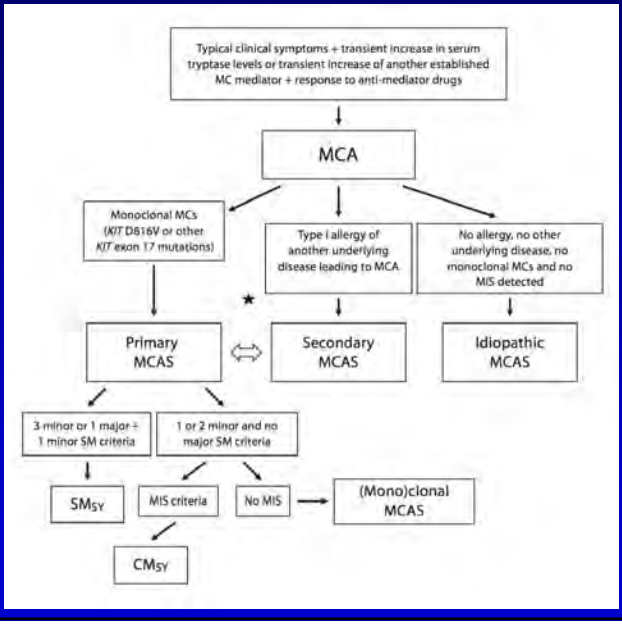
Diagnostic criteria for mast cell activation syndrome[a,7,10]

1. Signs and symptoms of mast cell activation involving at least 2 organ systems (eg, gastrointestinal: abdominal cramps, diarrhea; respiratory: broncho-spasm;
cardiovascular: hypotension or syncope; and skin: flushing, itching and less commonly urticaria and angioedema)
2. Increase in release of mast cell markers, such as tryptase, 24-hour urine histamine metabolites, or prostaglandin D_2 or its metabolite (11-β-prostaglandin F_2) with symptoms
3. Response in clinical symptoms to antimediator therapy

Lee and Akin. Ann Allergy Asthma Immunol 2013;111:5-8.

Algorithm for Diagnosis of MCAS

(Valent, Akin, Arock et al. Int Arch Allergy Immunol 2012;157:215-225)



Signs and Symptoms of MCAS (n=18)

(Hamilton et al. JACI 2011;128:147-52.)

Abdominal Pain	17 (94%)
Dermographism	16 (89%)
Flushing	16 (89%)
Headache	15 (83%)
Poor concentration/memory	12 (67%)
Diarrhea	12 (67%)
Naso-ocular	7 (39%)
Asthma	7 (39%)
Anaphylaxis	3 (17%)
Constellation of #1,2,3	13 (72%)

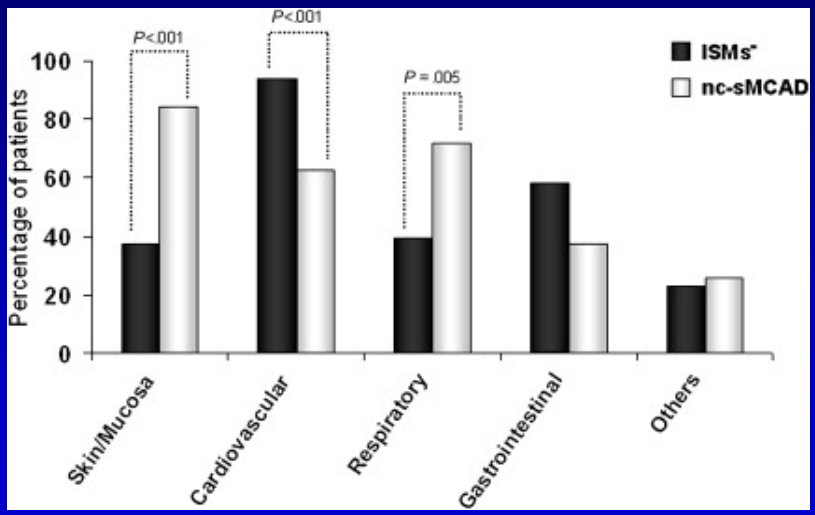
MCAS: A Consensus Proposal

(Valent, Akin, Arock et al. Int Arch Allergy Immunol 2012;157:215-225)

Table 3. Symptoms considered typical for MCA by the members

Symptom(s)	Consensus level
Flushing	95%
Pruritus	90%
Urticaria	85%
Angioedema	75%
Nasal congestion	90%
Nasal pruritus	90%
Wheezing	70%
Throat swelling	85%
Headache	90%
Hypotension	95%
Diarrhea	90%

Clinical Features of Mast Cell Disorders vs NC-ISM



(Alvarez-Twose et al. JACI 2010; 125:1269-1278.)

Mast Cell Activation Syndrome

(Hamilton MJ et al. JACI 2011;128:147.)

Table 3. Laboratory Mediators

Mast Cell Mediator	MCAS Patients Tested	# with (+) Test (% of total)	Mean (+) Level* (nml lab range)
Total serum tryptase (ng/ml)	17	5 (29)	10.7 ±3.7 (1-15)
24 hour urine histamine (nmol/g creatinine)	20	10 (50)	700 ±98 (0-386)
24 hour urine prostaglandin-D2 (ng/24 hour)	17	8 (47)	452 ±99 (100-280)
C-kit mutation (blood or bone marrow)	5	0 (0)	n/a

* ± standard error of the mean

MCAS: A Consensus Proposal

(Valent, Akin, Arock et al. Int Arch Allergy Immunol 2012;157:215-225)

Table 1. MC-derived mediators considered to contribute substantially to the clinical symptoms and manifestations of MCA

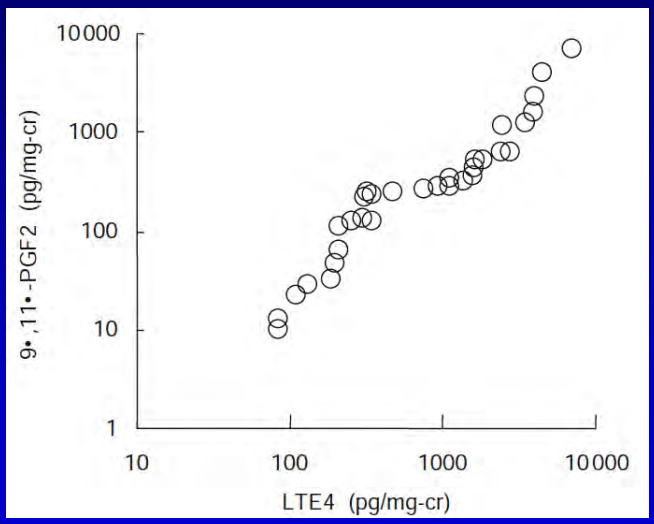
Mediator	Symptom(s)/sign(s)	Consensus level[1]
Histamine	headache, hypotension, urticaria with or without angioedema, pruritus, diarrhea	95%
PGD_2	mucus secretion, broncho-constriction, vascular instability	95%
PAF[2]	abdominal cramping, pulmonary edema, urticaria, bronchocon-striction, hypotension, arrythmia	90%
Proinflammatory cytokines	local inflammation, edema formation, leukocyte migration	80%
LTC_4 and LTD_4	mucus secretion, edema formation, vascular instability	80%
Chemokines	acute inflammation and leukocyte recruitment, leukocyte migration	70%
Tryptase	endothelial activation with con-secutive inflammatory reactions	65%

Mediators of Anaphylaxis

Mediators of Anaphylaxis

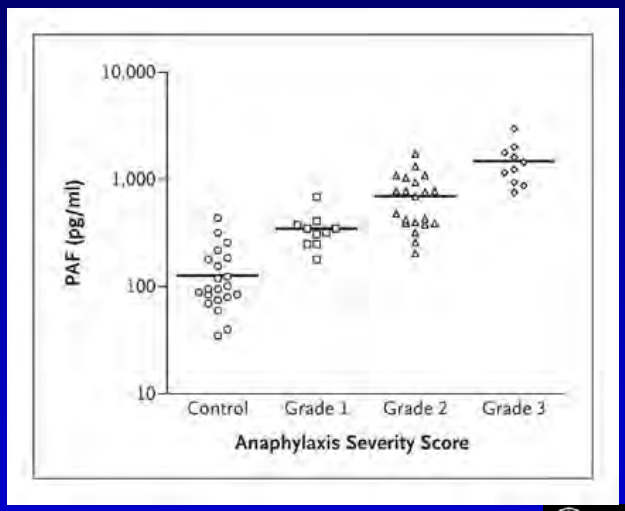
- Histamine
- Leukotrienes (LTC4)
- Prostaglandins (PGD2)
- Platelet Activating Factor (PAF)
- Carboxypeptidase
- Chymase
- Tryptase
- TNF alpha

Cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis.



Ono E et al. Clin Exp Allergy 2008;39:72-80.

Serum Platelet-Activating Factor (PAF) Levels as a Function of Anaphylaxis Severity Score

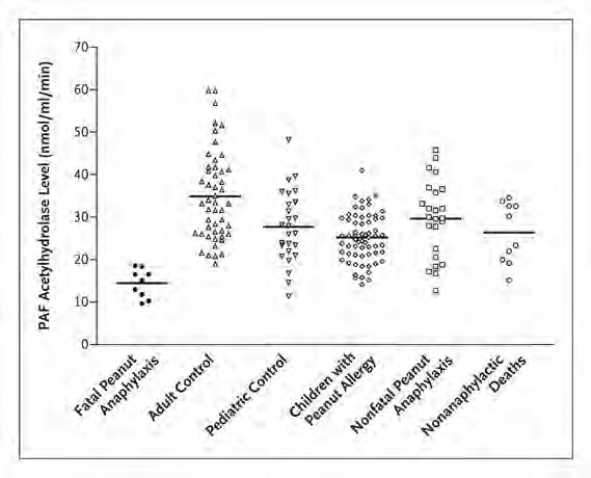


Vadas P et al. N Engl J Med 2008;358:28-35

The NEW ENGLAND JOURNAL of MEDICINE

Levels of Serum Platelet-Activating Factor (PAF) Acetylhydrolase Activity in Patients with Fatal Peanut Anaphylaxis and in Five Comparison Groups

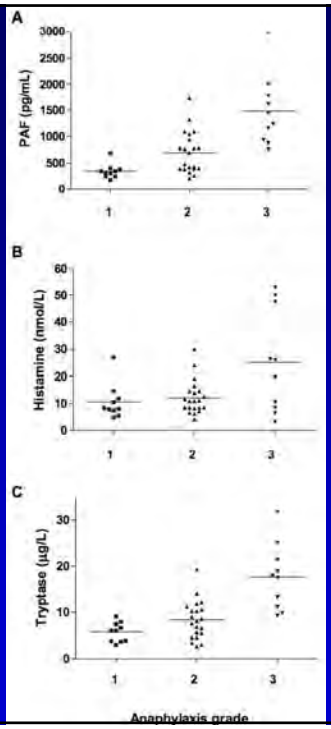
Vadas P et al. N Engl J Med 2008;358:28-35



Role of PAF in Anaphylaxis

(Vadas P, Ann Allergy Asthma Immunol 2016 (in press)

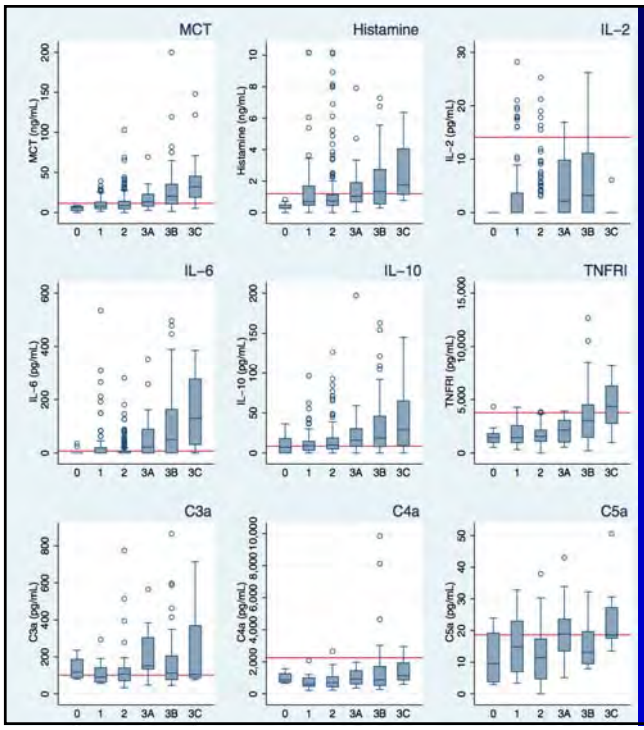
1. PAF reproduces the acute physiologic changes of anaphylaxis in experimental animals
2. PAF is produced acutely during anaphylaxis in both experimental animals and in humans
3. Circulating PAF levels correlate with the severity of anaphylaxis in animal models and in humans
4. Drugs that block the action of PAF prevent anaphylaxis in experimental animals
5. Mice engineered with a defective PAF receptor are resistant to anaphylaxis
6. Pretreatment with recombinant human PAF-AH protects against anaphylaxis.



Mediator in Human Anaphylaxis

Vadas, Perelman, Liss

JACI 2013;131:144-149.



Mediators in Human Anaphylaxis.

Brown S et al.

JACI 2013; 132:1141-1149

Non – IgE Human Anaphylaxis

Human IgE-independent anaphylaxis

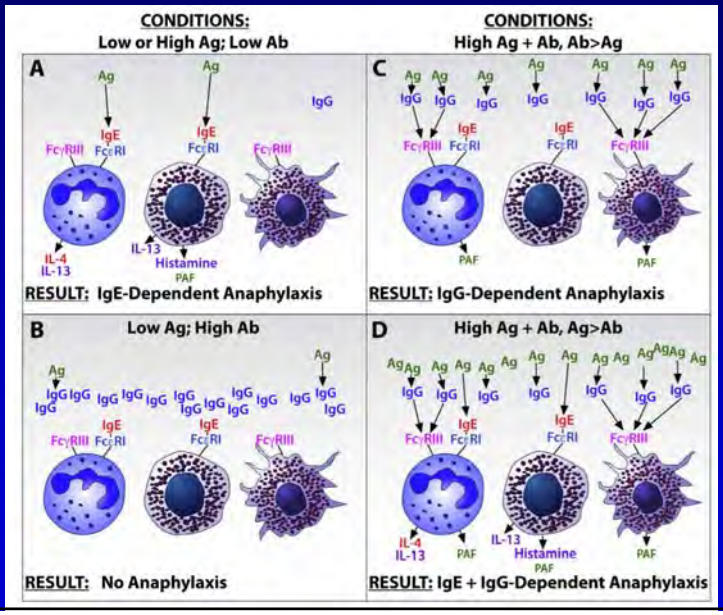
(Finkelman, Khodoun, Strait. JACI 2016;137:1674-80)

TABLE I. Etiologic mechanisms of anaphylaxis and their distinguishing characteristics

Type	Inciting agents	Cells	Receptors	Mediators
IgE mediated	Food allergy	Mast cells	FcεRI	Histamine
	Insect sting allergy	Basophils		PAF
	Drug allergy			
IgG mediated	Biologicals	Macrophages	FcγRIII	PAF
	Drugs	Neutrophils	FcγRI	Histamine
	Dextrans	Basophils	FcγRIV (mouse)	
	Aprotinin		FcγRIIA (human)	
	Transfusions			
Complement mediated	Lipid incipients	Macrophages	C3aR	PAF
	Micellar drugs	Mast cells	C5aR	Histamine
	Liposome			
	Other nanoparticles			
	Polyethylene glycol			
	Cellulose membranes			
Direct mast cell activation*	NSAIDs, including aspirin	Mast cells	MRGPRX2	Cysteinyl leukotrienes
	Vancomycin	Other myeloid cells	Other receptors	Histamine
	Opiates			
	Local anesthetics			
	Fluoroquinolone antibiotics			
	Neuromuscular blockers			
	Octreotide			
	Leuprolide			

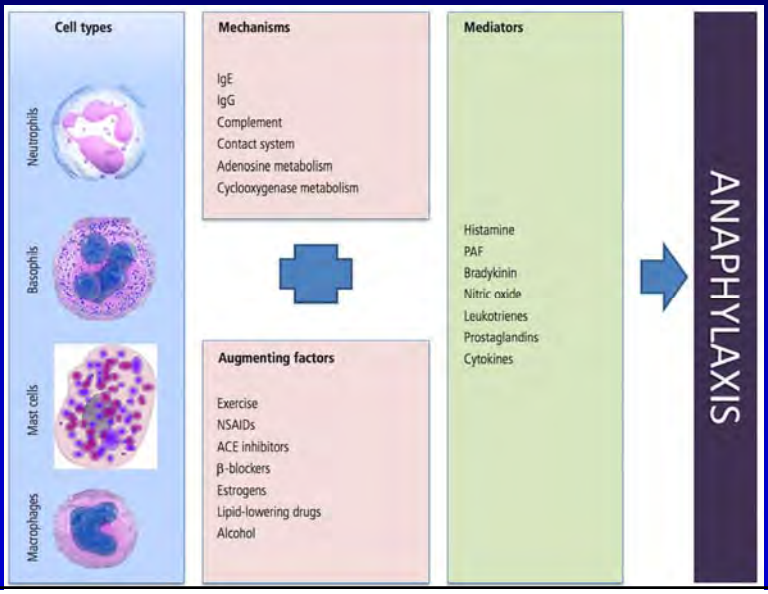
Human IgE-independent anaphylaxis

(Finkelman, Khodoun, Strait. JACI 2016;137:1674-80)



Non-IgE Mechanisms in Human Anaphylaxis

(Cano et al. Investig Allergol Clin Immunol 2016; 26: 73-82)



ACE Levels Affect Anaphylaxis

(Varney V et al. J Allergy (Cairo) 2012; doi: 10.1155/2012/258145)

Subject groups	Mean serum ACE levels U/L ± SD	*P* value V's HC (95% CI)	*P* value V's atopic (95% CI)	*P* value V's anaphylaxis group $n = 120$ (95% CI)
Healthy controls $N = 119$	48.9 ± 25		0.53	0.012 (3.4, 27.9)
Atopic controls $N = 49$	47.9 ± 25	0.86		0.018 (−16.1, −1.5)
Anaphylaxis $N = 118$	33.2 ± 20	0.012 (3.4, 27.9)	0.018 (−16.1, −1.5)	
CRA* $N = 27$	35.1 ± 25	0.031 (1.14, 24.3)	0.025 (1.6, 25.9)	0.23
AACVS† $N = 93$	31.2 ± 20	0.015 (1.72, 15.5)	0.011 (2.2, 17.1)	0.81

*Cutaneous and respiratory allergy.
†Acute angioedema and cardiovascular collapse.

When to Prescribe Epinephrine Autoinjector ?

Controversies and Unsettled Issues:

- Immunotherapy
- Oral allergy syndrome
- Facial contact urticaria (food)
- Skin or GI reactions
- Elderly cardiac patient
- LLR to stings