Anaphylaxis

DDx & Diagnostic Studies

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Disclosure Statement

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I participate in the following Speaker's Bureau and/ or Advisory Boards:

- **Myland Labs**
- **TEVA**
- **Sunovian**
- **Sanofi**

EPIDEMIOLOGY OF ANAPHYLAXIS

- At Risk: 1% to 15% of the population (US data[1])
  Prevalence: Estaimated that up to 2% of population BUT UNDERDIAGNOSED!
- Up to 1% of patients with anaphylaxis may die
- Fatalities per year in the US:
  - Food-induced: 150
  - Antibiotic-induced: 600
  - Venom-induced: 50
- Food allergy affects up to 6%-8% of children younger than 4 years of age and 2% of the US population beyond the 1st decade of life[3,4]
- Incidence of anaphylaxis is increasing[5]

1. Neugut et al. *Arch Int Med* 2001 2. Yocum et al. *J Allergy Clin Immunol* 1999 3. Sampson H. *N Engl J Med* 2002
4 Sampson et al. *J Allergy Clin Immunol* 2006 5.. Sheikh et al. *BMJ* 2006 6. Kemp SF and Lockey JACI 2002;110:341-8

Learning Objectives

- At the conclusion of this lecture the attendee should be able to:
  - **Discuss how to recognize anaphylaxis**
  - **List the major causes of anaphylaxis**
  - **Cite the common disorders in the differential of anaphylaxis**
  - **Describe the diagnostic tests used to diagnose anaphylaxis and the disorders that mimic anaphylaxis**

Clinical Criteria for Anaphylaxis

Anaphylaxis is likely if 1 or 3 set of criteria are fulfilled

1 **Acute onset (min to hrs)**

- **Skin/mucosal symptoms**

AND

- **Airway compromise**

OR

- **↓ BP or Associated symptoms**

2 Exposure to known allergen + at least 2 items below within min to hrs

- ~~Hx of severe reaction~~ (2006)
- Skin/mucosal symptoms
- Airway compromise
- ↓ BP or Associated symptoms
- GI symptoms with food allergy

3 Hypotension within min. to hrs. after exposure to known allergen

Symposium on the Definition and Management of Anaphylaxis: Summary report. Sampson HA, et al. JACI 2005; 115:584-59. Second symposium on the definition and management of anaphylaxis: summary report. Sampson HA, et al. JACI 2006; **117**(2): p. 391-7.

"ANAPHYLAXIS" FUNCTIONAL DEFINITION

- *"If you suspect that you (or a patient) are having an acute allergic reaction, regardless of the severity of the presenting symptoms, treat it as anaphylaxis with IM epinephrine immediately."*

Frequency and 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

Lieberman P, et al. *J Allergy Clin Immunol.* 2010;126:477-480.

If there is no cutaneous involvement, question the diagnosis of anaphylaxis.

- Signs and symptoms: usually within 5 to 30 minutes
- More rapid onset, more serious the reaction

Agents that cause anaphylaxis anaphylactic (IgE-dependent)

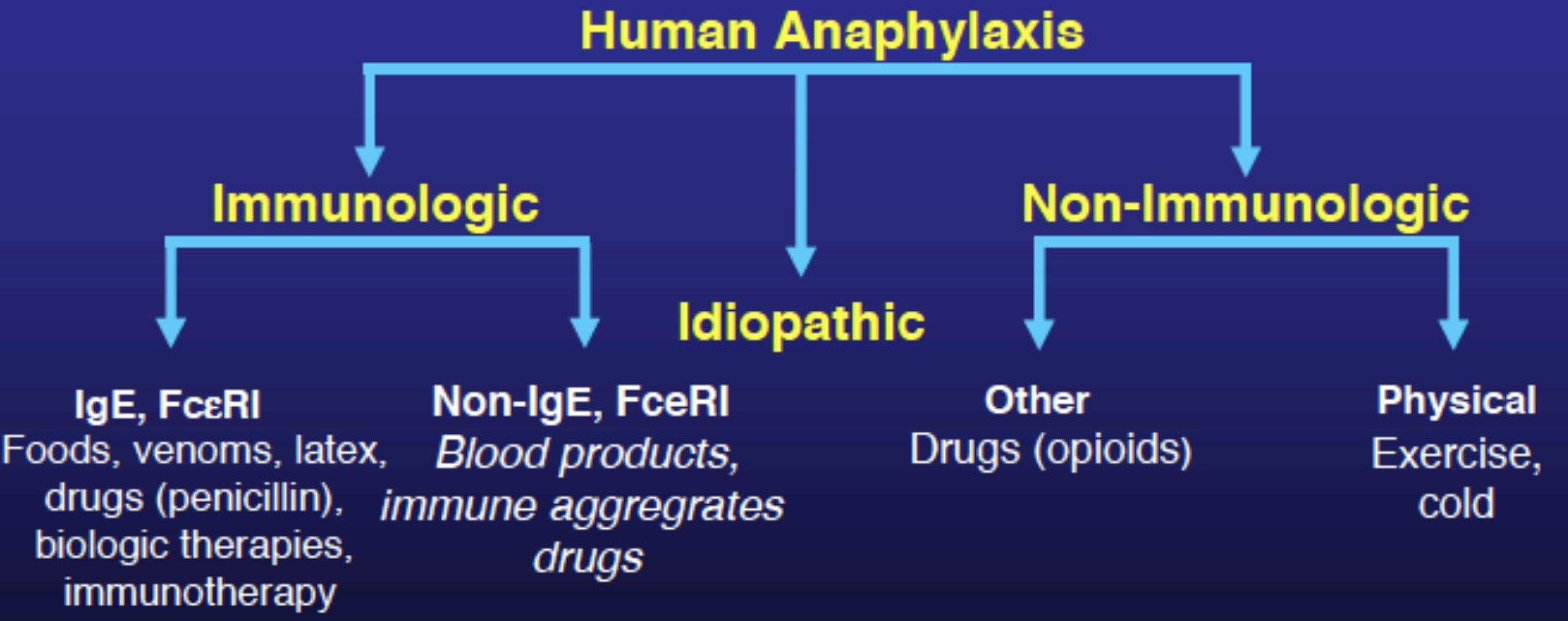
- Foods (peanut, tree nuts, and crustaceans, milk, egg and fish)
- Medications (antibiotics)
- Venoms
- Latex
- Allergen vaccines
- Hormones
- Animal or human proteins
- Diagnostic allergens
- Muscle relaxants
- Colorants (insect-derived, such as carmine)
- Enzymes
- Polysaccharides
- Aspirin and other non-steroidal anti-inflammatory drugs (probably)
- Exercise (possibly, in food and medication-dependent events)

Kemp Immunol Allergy Clin N Am 2001

New causes of IgE-mediated Anaphylaxis

- Chemotherapy drugs
- Monoclonal antibodies
  - Tissue necrosis factor
  - Epidermal growth factor
  - Anti-IgE (omalizumab)
- Solvent used in chemotherapy drugs, e.g. Cremophor-L

Mechanisms of Human Anaphylaxis



IgE=immunoglobulin E;
FcεRI=high-affinity IgE receptor;

Simons FER, et al. *J Allergy Clin Immunol*. 2010;125:S161-S181.

Agents that cause anaphylaxis (Allergic but not IgE mediated)

Immune aggregates (Type II)

- Intravenous immunoglobulin
- Dextran (possibly)

Cytotoxic (Type III)

- Transfusion reactions to cellular elements (IgG, IgM)

Kemp Immunol Allergy Clin N Am 2001

ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

MULTIMEDIATOR COMPLEMENT ACTIVATION/ACTIVATION OF CONTACT SYSTEM

- Radio-contrast media
- Over-sulfated chondroitin sulfate (OSCS) in heparin
- Renal dialysis with sulfonated polyacrylonitrile, cuprophane, or polymethylmethacrylate dialysis membranes
- Ethylene oxide gas on dialysis tubing (possibly through IgE)
- Protamine

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8

ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

NONSPECIFIC DEGRANULATION OF MAST CELLS AND BASOPHILS

- Opiates
- Physical factors:
  - exercise (no food or medication co-trigger)
  - temperature (cold, heat)

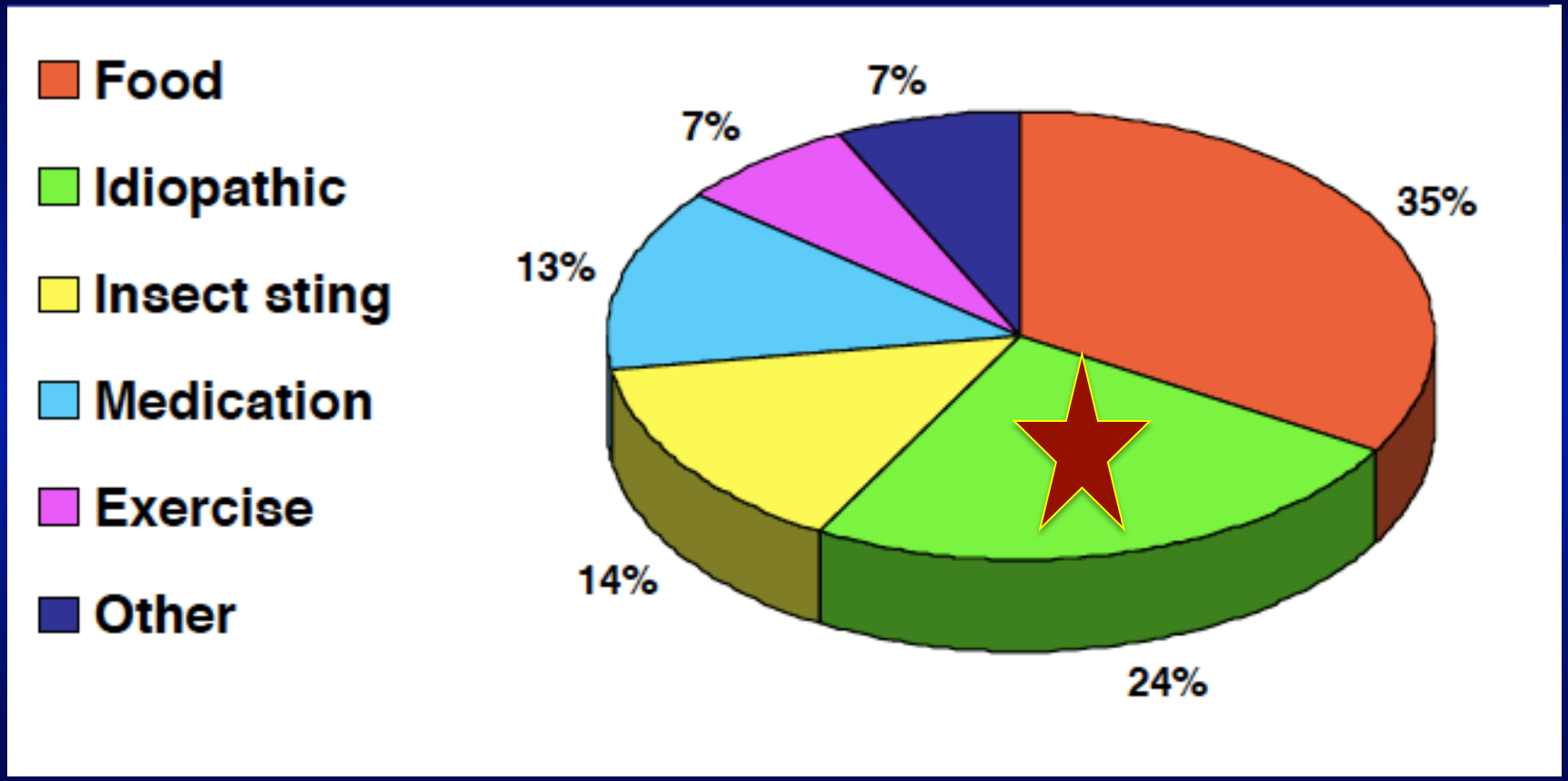
Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8

IDIOPATHIC ANAPHYLAXIS

- Common in adults referred to allergists for anaphylaxis
- Uncommon in children
- Negative skin tests, negative dietary history, no associated diseases eg. mastocytosis
- Preventive medication: oral corticosteroids, H_1 & H_2 antihistamines, anti-leukotrienes
- Deaths rare
- May gradually improve over time

Lieberman PL JACI 2005: 115: S483-523

Causes of Anaphylaxis

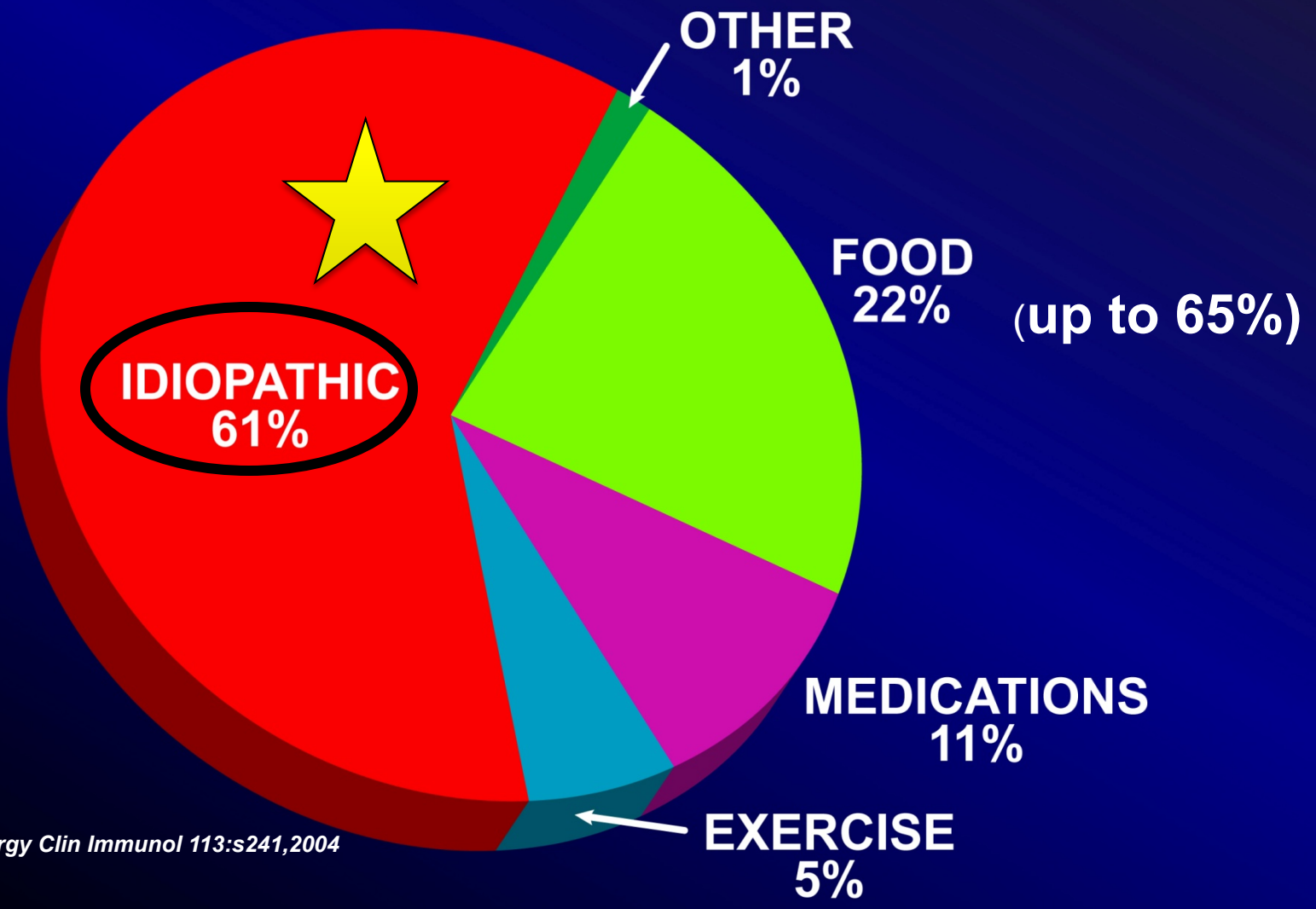


Yocum, MW, Khan DA, Mayo Clin Proc 69:16-23, 1994

The Causes of Anaphylaxis:

Select Cases (1002)

Venom ?? 11-21%



Webb et al:J Allergy Clin Immunol 113:s241,2004

Anaphylaxis DDx
Common Disorders

- Asthma- acute episode {consider trigger}
- Acute generalized urticaria
- Acute angioedema
- Vasovagal reaction (fainting)
- Panic attack/acute anxiety/hyperventilation
- Vocal cord dysfunction
- Cardiovascular event
  - Coronary artery syndrome/infarction
  - Pulmonary embolus
- Neurological event, e.g. CVA, seizure

Anaphylaxis vs.. Vasovagal

Anaphylaxis

- Hypotension
- Tachycardia
  - ↓ (several minutes after onset)
  - Bradycardia (with ↓ BP)
- Cutaneous manifestations (urticaria, **flush**, pruritus)

Vasovagal

- Hypotension
- Bradycardia (immediately)
- **Pallor**
- Weakness
- Nausea & vomiting
- Diaphoresis
- No cutaneous symptoms
- Relieved by recumbency

Anaphylaxis vs.. Panic/anxiety

ANAPHYLAXIS

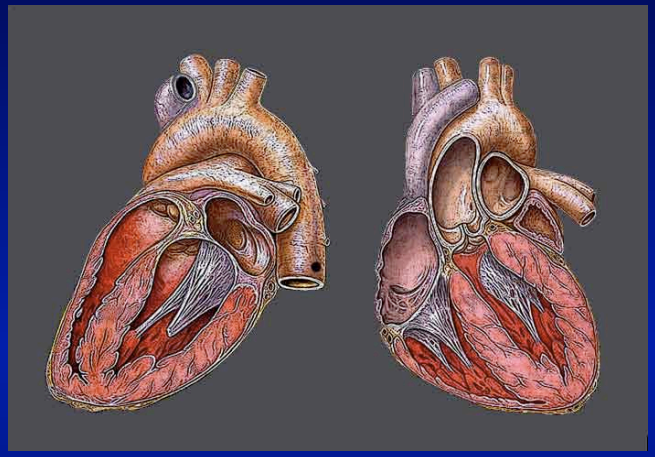
- *Impending doom*
- *Flushing*
- *Chest pain*
- Cough
- Wheeze
- Itching
- Urticaria
- Angioedema
- Hoarseness
- Stridor
- Hypotension or LOC

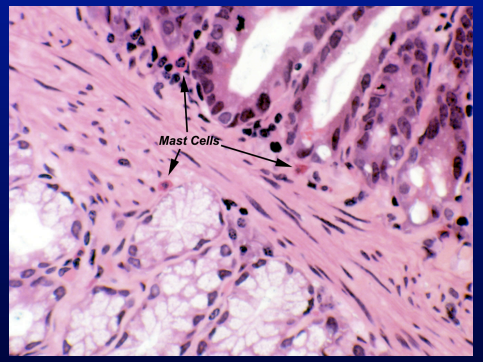
PANIC/ANXIETY

- *Impending doom*
- *Flushing*
- *Chest pain*
- Sweating
- Breathlessness without wheeze
- Trembling/palpitations
- Gastrointestinal symptoms
- Globus sensation
- Tingling/numbness of extremities
- Feeling faint

Acute Coronary Syndrome or Severe Anaphylaxis

- 68 near **fatal reactions** to immunotherapy
  - 80% with hypotension
- **15% present of** anaphylaxis present with **chest pain**
- **Histamine can induce coronary spasm in nl patients**
- **7%** present with an **arrhythmia**
- **Increased # of heart mast cells with ischemic heart dx**





Lieberman P et al. The diagnosis and management of anaphylaxis practice parameter: 2010 Update. J Allergy Clin Immunol. 2010 Aug 6.
[Epub ahead of print] PubMed PMID: 20692689.) . (AKA 2010 JTF Anaphylaxis PP)

Vocal Cord Dysfunction

- Presents as inspiratory AND expiratory upper airway stridor- heard most at neck level
- Dyspnea, cough, & expiratory wheeze may be present
- Patient has sensation of upper airway swelling
- Direct fiberoptic laryngoscopy may be required for diagnosis
- Intermittent adduction of the anterior vocal chords during inspiration
- No uvular edema
- Abnormal inspiratory flow volume loop

Less Common Differential Diagnosis for Anaphylaxis

Anaphylaxis DDx
Eating associated syndromes

- Monosodium glutamate
- Sulfites
- Scombroid poisoning
- Anisakiasis
- Food poisoning (usually GI tract only)
- Pollen-food allergy syndrome
- Foreign body aspiration/choking

Scombroidosis

- Histamine fish poisoning- occurs 15-90 minutes after eating spoiled fish
- Tuna, mackerel, mahi mahi, sardines, anchovies, herring, etc.
- Flushing, headache, N & V, diarrhea, abdominal pain, dysphagia, palpitations, dizziness, hypotension
- Rarely urticaria and itching
- Elevated serum histamine but normal tryptase
- Negative sIgE to the fish

Anisakiasis- True Allergy

- IgE response to Anisakis simplex fish parasite
- Found in raw or undercooked saltwater fish
- Onset up to 24 hours after ingestion
- Elevated serum sIgE to Anisakis (Ani s 7)
- Negative sIgE to the fish

POLLEN FOOD ALLERGY SYNDROME

Birch

Apple Peach Plum Pear Cherry Apricot Almond

Rosaceae

Carrot Celery Parsley Caraway Fennel Coriander Aniseed

Apiaceae

Soybean Peanut Hazelnut

Fabaceae **Betulaceae**

(old Leguminosae)

Ragweed

Cantaloupe Honeydew Watermelon Zucchini Cucumber

Cucurbitaceae

Banana

Musaceae

Pollen food allergy syndrome or oral allergy syndrome (OAS)

- Oral mucosal itching, swelling, tingling
- Elicited by a variety of plant proteins that cross-react with airborne allergens
- Pollen allergic patients may develop symptoms following the ingestion of vegetables foods:
  - *Ragweed* allergic patients: *Fresh melons and bananas*
  - *Birch pollen* allergic patients: *Carrots, celery, apples, pears, hazelnuts and kiwi*
- Immunotherapy for treating the pollen-induced rhinitis may or may not reduce oral allergy symptoms

J Allergy Clin Immunol. 2004; 113:808-809

Components of Pollen Food Allergy Syndrome (PFAS)

- A history of symptoms consistent with PFAS
- Allergic sensitization to pollen
- Allergic sensitization to a plant food
- A known correlation between the plant food and the pollen

Pollen Food Allergy Syndrome (PFAS)
Oral Allergy Syndrome + systemic reactions

- PFAS emphasizes that one may have not only oropharyngeal symptoms but systemic symptoms 2-10% of the time
- While usually associated only with raw foods, cooked plant foods may provoke the PFAS
- Prick-by-prick testing to fresh food is preferred for most fruits and vegetables
- Stable allergens, e.g. peanut, hazelnut, and pea may be best detected with commercial extracts
- Consider duplicate testing when extracts are available

Anaphylaxis DDx
Flush Syndromes

- Peri-menopause- lasts < 5 minutes, often associated with sweating
- Autonomic epilepsy
- Alcohol induced, e.g. enzyme mediated, Hodgkin's, sulfites, disulfram, chlorpropamide & other meds
- Medication induced, e.g. niacin
- Carcinoid syndrome
- Gastrointestinal VIpomas
- Medullary carcinoma of the thyroid

Carcinoid Syndrome

- Tumors secrete:
  - Serotonin
  - Substance P
  - Other vasoactive chemicals
- Tumors – most common in small bowel, appendix, or colon
- Episodic (20-30 seconds) of red to purple flushing, at times with burning sensation of face, neck, upper chest
- Diarrhea common
- Wheezing at times

Gastrointestinal Tumors

- Secrete:
  - Vasoactive Intestinal peptides
  - Substance P
- Very rare
- Symptoms of watery diarrhea, ↓ Na & Cl
- 20% associated with flushing

Carcinoid & VIpomas

- Diagnostic tests for carinoma:
  - Plasma serotonin
  - 24 hour urine for 5-hydroxyindoleacetic acid
  - Pt must avoid foods high in serotonin and tryptophan
    - **bananas, plums, pineapple and its juice, kiwi, avocados, eggplant, any tomato products and nuts (especially walnuts), chocolate, tea, coffee**
- Diagnostic test Vipomas:
  - Substance P
  - Vasoactive peptides

Anaphylaxis DDx
Shock syndromes

- Hypovolemic
- Cardiogenic
- Septic
- Distributive

Anaphylaxis DDx
Other

- Hereditary or acquired angioedema/C-1 esterase deficiency- Type l, ll, lll
- ACE inhibitor induced angioedema
- Red man syndrome (Vancomycin)
- Pheochromocytoma
- Systemic capillary leak syndrome

Hereditary or acquired angioedema

- Not associated with itching or hives
- Often unilateral
- Face/tongue/extremities/genitalia/bowel wall
- Can be associated with abdominal pain/ vomiting/diarrhea/hypovolemic shock
- Associated with reduced C4
- C1-esterase inhibitor is deficient quantitatively &/or functionally

Anaphylaxis DDx
Mast cell clonal disorders

- Skin mastocytosis
- Systemic mastocytosis
- Mast cell activation syndrome
- Indolent systemic mastocytosis
- Mast cell or basophilic leukemia
- Mast cell sarcoma
- Extra cutaneous mastocytoma

Systemic Mastocytosis Dx (WHO)

- **The presence of one major +1 minor criteria or 3 minor criteria constitute the diagnosis of systemic mastocytosis.**
  - **Major: Biopsy finding of multiple dense accumulations of mast cells in bone marrow or in other non-skin tissue.**
  - **Minor:**
    - **>25% mast cells in BM biopsy are spindle-shaped or atypical on BM smear**
    - **Point mutation at codon 816 in kit receptor gene**
    - **Surface kit receptor + CD2 or CD 25 on mast cells**
    - **Serum total tryptase persistently > 20 ng/ml**

NOTE: 80% have Urticaria Pigmentosa, most have low IgE levels

Mast Cell Activation Syndrome

- **No established diagnostic criteria** (fails to fulfill SM criteria) and lacks BM clusters of mast cells
- Inappropriate release of mast cell mediators causes **recurrent syncope** or presyncope associated with hypotension, flushing, & abdominal symptoms
- Clonal CD25+ MCs carrying D816V c-kit mutation
- **Tryptase usually >11. 4 but <20 ng/ml**
- BM biopsy that contains a **normal number of mast cells**
- No Urticaria pigmentosa, rare hives, + flushing and itching
- 20-40% of cases of recurrent anaphylaxis have MCAS
- Does not seem to progress to systemic mastocytosis

Pheochromocytoma

- Catecholamine-secreting tumors (adrenal medulla)
- Episodic headache, sweating, and tachycardia
- Pallor during episode
- Hypertension is typical but hypotension is possible
- 24 hour urine for metanephrines, vanillylmandelic acid, and catecholamines
- Plasma levels of catecholamines and free metanephrines
- CT and MRI of adrenal gland

Capillary Leak Syndrome

- Rare and often fatal
- Recurrent episodes of angioedema, GI symptoms, and shock
- Hemoconcentration during hypotensive episode
- Monoclonal gammopathy
- Treat with fluid resuscitation and supportive care

DIAGNOSTIC STUDIES

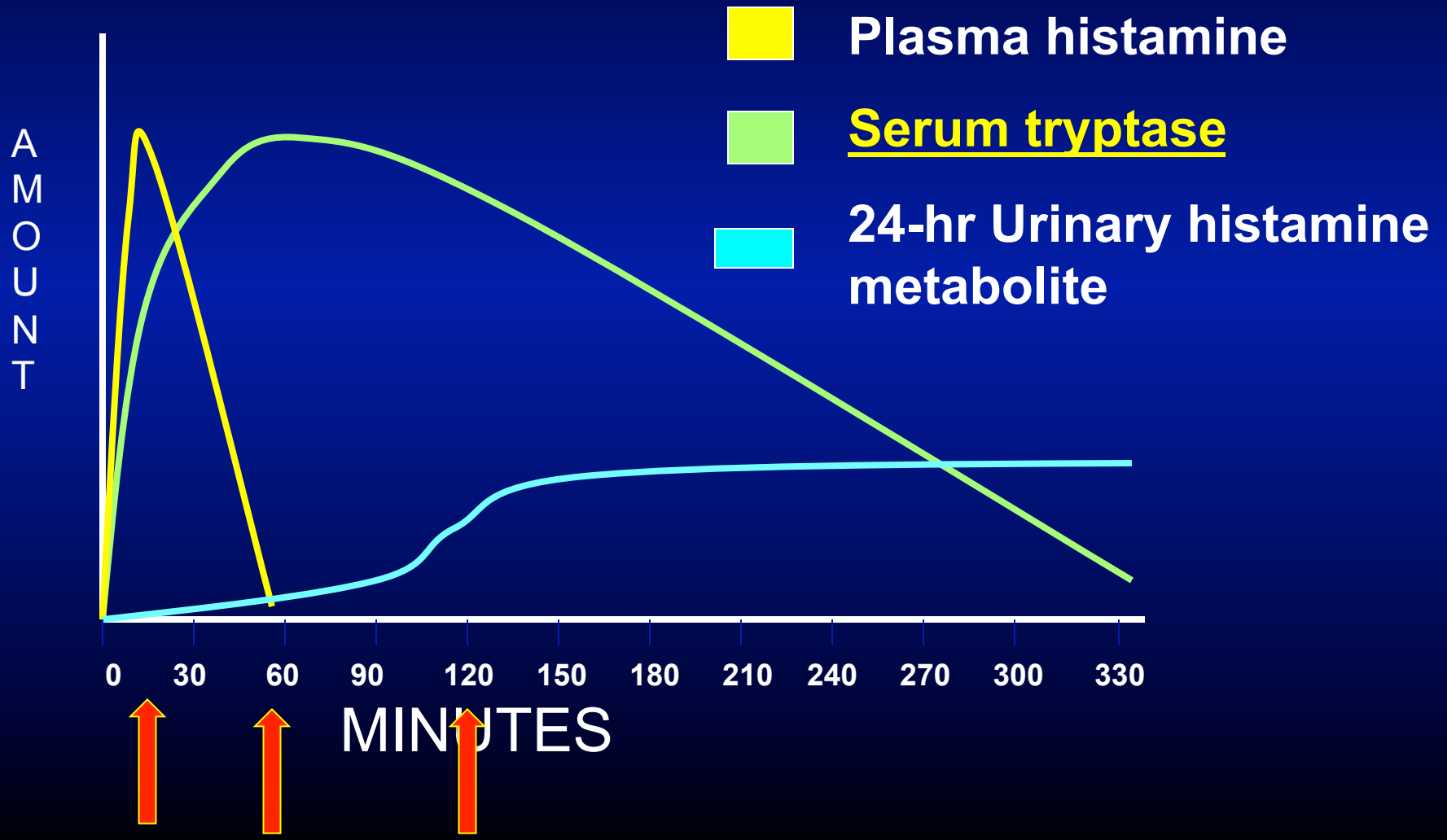
Determining the sIgE Anaphylaxis triggers

- Skin testing/sIgE serum testing for suspected
  - Foods
  - Stinging Insects
  - Biting insects
  - Medications
  - Latex
- Prick/prick testing of foods
- Consider oral challenge to a food or drug with the trigger is suspected but not established

Diagnostic lab markers

- **Tryptase**
- Histamine
- Prostaglandin D2
- Carboxypeptidase
- CD63
- IL-4 and IL-6

LABORATORY TESTS IN THE DIAGNOSIS OF ANAPHYLAXIS



Serum Tryptase

- **Total tryptase** (pro-β + β)
  - Starts to ↑ 5-10 minutes
  - Peaks 15-60 minutes (venom sting)
  - Remains elevated 4-6 hours following anaphylaxis
- Baseline tryptase is mainly **pro-beta**
- **β tryptase** (mature) ↑ during anaphylaxis
- Best measurement is mature/total tryptase ratio*
- **Total Serum Tryptase is only commercial test available**

* Dr. Larry Schwartz lab, Virginia Commonwealth University

1. J Clin Invest 83: 1551, 1989

SERUM TRYPTASE

- Histamine and tryptase levels may not correlate
- Tryptase higher if allergen administered parenterally (hymenoptera or injections) than orally (foods)
- Tryptase: Connective tissue mast cells> Mucosal mast cells (MC degranulation $\Rightarrow$ β tryptase)
- Ratio Total Tryptase(α+ β) / β <10: Anaphylaxis
- If > 20 indicates systemic mastocytosis
- In ideal conditions, positive predictive value of serum tryptase can be 92.6%, but negative predictive value is only 52%
-

Lin RY et al. J Allergy Clin Immunol 2000;106:65-71

Serum Tryptase

- Single serum tryptase has low sensitivity
- Total serum tryptase in anaphylaxis may remain within nl range
- 15 & 60 min post venom sting, a > 2 ng/ml increase showed a 0.73 sensitivity & 0.98 specificity for dx of anaphylaxis[1]
- **Usually not ↑ in food-induced anaphylaxis**
- ↑ more likely in hypotensive anaphylaxis
- Obtain in idiopathic anaphylaxis to R/O Mast cell dz

* Dr. Larry Schwartz lab, Virginia Commonwealth University

1. Brown SG et al. Emerg Med Austral 2004; 16:120

Serum Tryptase Elevation

- Anaphylaxis (esp. venom & IV meds, hypotension)
- Scombroid poisoning
- Myocardial infarction
- Mast cell clonal disorders
- Acute Myelocytic Leukemia

Histamine and other Biomarkers

- Plasma histamine begins to rise in 5 minutes but remains elevated for only 30 to 60 minutes.
- Draw blood with large bore needle, keep at 4°C and centrifuge promptly and freeze plasma
- Urinary histamine metabolites may remain elevated as long as 24 hours. (24 hour urinary histamine and N-methylhistamine).
- Blood tests for other biomarkers, such as carboxypeptidase A3 and platelet-activating factor are reported but remain experimental

Simons E et al. JACI 2007;120:S2-24

Additional tests to consider

- Complement levels
- Urinary histamine
- Skin biopsy, even non-lesional skin if mast cell syndromes suspected
- Bone Marrow biopsy

Additional Objective Tests to Consider in the Differential Diagnosis of Anaphylaxis

To Be Measured	Comment
Plasma histamine	Plasma histamine levels begin to rise within 5-10 min and remain elevated only for 30-60 min. They are of little help if the patient is seen as long as an hour or more after the onset of the event.
24-Hour urinary histamine metabolite (methyl histamine) of time	Urinary histamine and its metabolites are elevated for longer period; up to 24 hours
Plasma-free metanephrine	To rule out a paradoxical response to a pheochromocytoma
Serum serotonin	To rule out carcinoid syndrome
Urinary 5-hydroxyindoleacetic acid	Also to rule out carcinoid syndrome
Serum vasointestinal hormonal polypeptide panel including pancreastatin, pancreatic hormone, vasointestinal polypeptide, and substance P	Useful to rule out the presence of a vasoactive polypeptide-secreting gastrointestinal tumor or a medullary carcinoma of the thyroid, which also can secrete vasoactive peptides

Lieberman P, et al. *J Allergy Clin Immunol.* 2010;126:477-480.

JTF Anaphylaxis PP

Practice parameter

The diagnosis and management of anaphylaxis practice parameter: 2010 Update

Chief Editors: **Phillip Lieberman, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Stephen F. Kemp, MD,** and **David M. Lang, MD**

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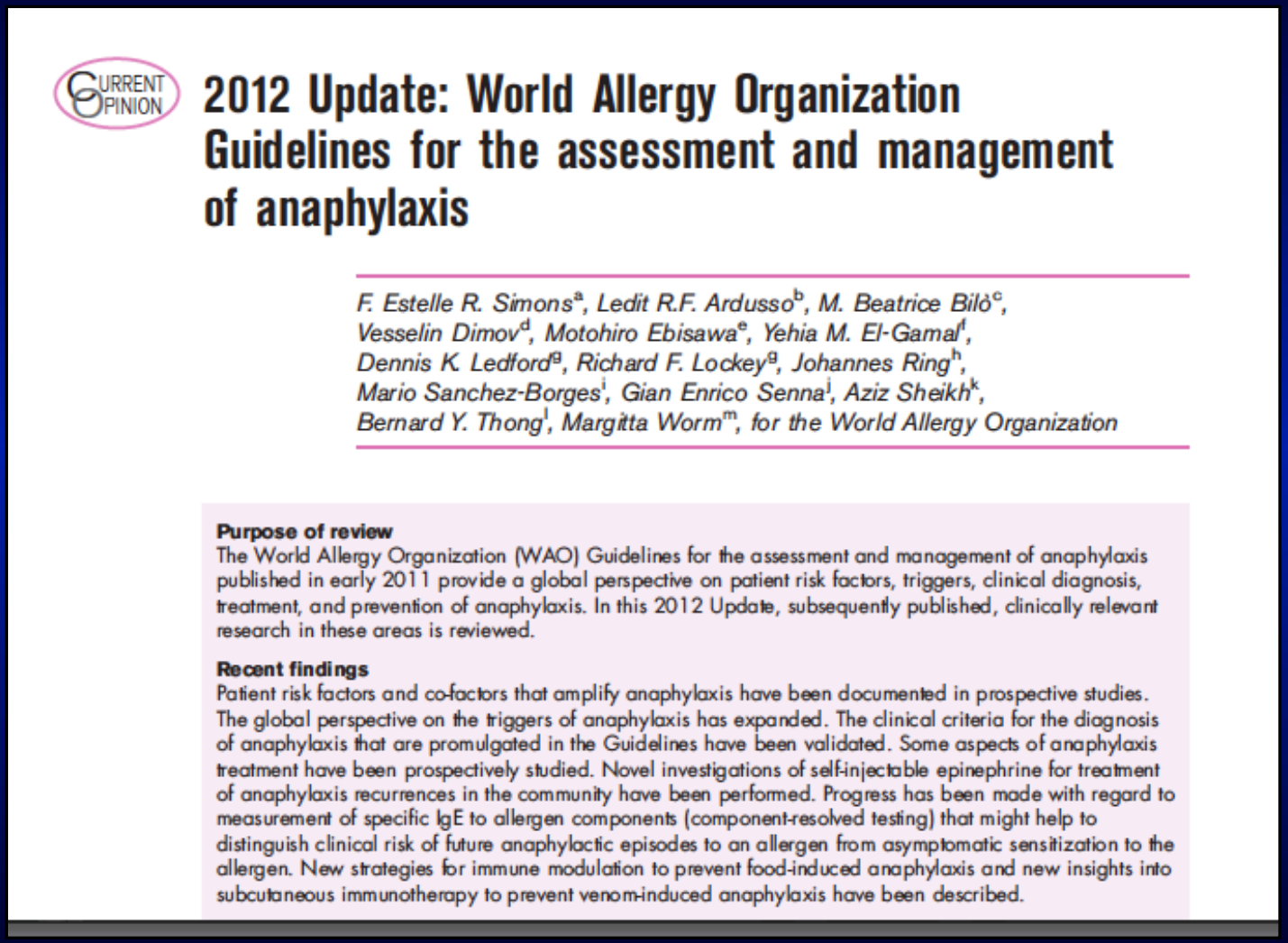
These recommendations are also reflected in previous position statements/guidelines from the World Allergy Organization (2008) and the Canadian Pediatric Society Allergy Section (1998).

Lieberman P, et al. *J Allergy Clin Immunol.* 2010;126:477-480.

WAO Anaphylaxis Guidelines



CURRENT OPINION

2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis

F. Estelle R. Simons[a], Ledit R.F. Ardusso[b], M. Beatrice Bilò[c], Vesselin Dimov[d], Motohiro Ebisawa[e], Yehia M. El-Gamal[f], Dennis K. Ledford[g], Richard F. Lockey[g], Johannes Ring[h], Mario Sanchez-Borges[i], Gian Enrico Senna[j], Aziz Sheikh[k], Bernard Y. Thong[l], Margitta Worm[m], for the World Allergy Organization

Purpose of review

The World Allergy Organization (WAO) Guidelines for the assessment and management of anaphylaxis published in early 2011 provide a global perspective on patient risk factors, triggers, clinical diagnosis, treatment, and prevention of anaphylaxis. In this 2012 Update, subsequently published, clinically relevant research in these areas is reviewed.

Recent findings

Patient risk factors and co-factors that amplify anaphylaxis have been documented in prospective studies. The global perspective on the triggers of anaphylaxis has expanded. The clinical criteria for the diagnosis of anaphylaxis that are promulgated in the Guidelines have been validated. Some aspects of anaphylaxis treatment have been prospectively studied. Novel investigations of self-injectable epinephrine for treatment of anaphylaxis recurrences in the community have been performed. Progress has been made with regard to measurement of specific IgE to allergen components (component-resolved testing) that might help to distinguish clinical risk of future anaphylactic episodes to an allergen from asymptomatic sensitization to the allergen. New strategies for immune modulation to prevent food-induced anaphylaxis and new insights into subcutaneous immunotherapy to prevent venom-induced anaphylaxis have been described.

Current Opinion in Allergy & Clinical Immunology. 2012; 12(4): 389-399.

We Must Prevent Death from Anaphylaxis