# Anaphylaxis... a conversation with your patient



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### Presenter Disclosure

- Faculty: Dr. Thomas Gerstner, MD, FRCP(C)
- Relationships with commercial interests:
  - Grants/Research Support: Merck
  - Speakers Bureau/Honoraria: Pfizer, Mylan
- The program focuses on the appropriate management strategies for acute and long-term treatment of patients at risk for anaphylaxis.
- I had full control over the content of this presentation.
- All recommendations are evidence-based and all sources of scientific research are referenced.

# Learning Objectives: Anaphylaxis

- Describe the pathogenesis and list major causes of anaphylaxis
- Describe recent prevalence trends
- Identify the patients at-risk
- Implement appropriate management strategies for acute and long-term treatment, including:
  - Acute care and epinephrine auto-injector use
  - Diagnostic testing
  - Addressing patient education gaps
  - New potential therapeutic options

#### Pretest: Question 1

Which of the following is part of the differential diagnosis in cases of suspected anaphylaxis?

1.Panic attacks

- 2.Vasovagal reactions
- 3.Flushing syndromes
- 4. Urticaria
- 5.Only #2 and #4
- 6.All of the above

#### Pretest: Question 2

The presence of which of the following increases the risk for more severe anaphylactic reactions?

1. Atopic dermatitis

- 2.Allergic rhinitis
- 3.Asthma
- 4.None of the above

Pretest: Question 3 Which of the following statements about anaphylaxis is TRUE?

A) The most frequent signs of anaphylaxis are wheezing and dyspnea.

B) Symptoms can recur several hours after they have resolved

C) Fatality rates from food induced anaphylaxis are increasing

D) Most symptoms of anaphylaxis occur within one minute after accidental ingestion.

Anaphylaxis is more common in children compared to adults

1. True

2. False

Death from anaphylaxis is more likely to occur in children than adults

- 1. True
- 2. False

Peanut allergy is not outgrown

1. True

2. False

Allergic reactions to food tend to become more serious with each exposure

- 1. True
- 2. False

Following an allergic reaction, administration of epinephrine in the ER is as effective as using it (in an autoinjector) beforehand

- 1. True
- 2. False

Antihistamines when used early help reduce the severity of anaphylaxis

- 1. True
- 2. False

The Epipen autoinjector, once injected, should be held in place for 10 seconds for optimal delivery of medication

- 1. True
- 2. False

Those with severe peanut allergy may react from inhalation of the aroma of peanut butter nearby

- 1. True
- 2. False

Those with peanut allergy may develop anaphylaxis from direct skin contact with peanut butter

- 1. True
- 2. False

Sharks can be allergic to peanut butter ??

- 1. Yes
- 2. No

# Definition of Anaphylaxis

- A serious allergic reaction
- Rapid in onset
- May cause death

# Anaphylaxis is Highly Likely When 1 of the Following 3 Criteria Are Fulfilled:

- 1. Acute onset (minutes to several hours) with involvement of the skin, mucosal tissue, or both (*e.g.*, generalized hives, pruritus or flushing, swollen lips-tongue-vulva) AND AT LEAST ONE OF THE FOLLOWING:
  - respiratory compromise
  - cardiovascular compromise (hypotension, palpitations, collapse)
- 2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for that patient:
  - involvement of the skin/mucosal tissue
  - respiratory compromise
  - reduced BP or associated symptoms
  - persistent gastrointestinal symptoms
- 3. Reduced BP after exposure to known allergen (minutes to several hours)
  - infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP
  - adults: systolic BP < 90 mm Hg or > 30% decrease from patient' s baseline values

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  - cardiovascular compromise: reduced BP or associated symptoms
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#### Sampson et al. JACI 2006; 117(2):391-7.

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#### Samantha

- Samantha is a 13-year-old girl who eating lunch at a restaurant patio, which included a pecan salad and shrimp stir fry
- Within minutes, she developed dizziness, shortness of breath, wheeze, and a generalized raised skin rash
- Her family rushed her to the emergency room, when she vomited twice enroute

- Is this anaphylaxis?
  - Skin rash (hives), shortness of breath/wheeze, emesis
- Possible triggers?
  - Tree nuts (pecan), shellfish (shrimp stir-fry)
  - •? Other contaminating nuts, fish
  - •? Venom sting
  - ? Medications

## **Differential Diagnosis**

- Vasovagal reaction
- Acute asthma attack
- Panic attack
- Acute urticaria
- Laryngospasm (and vocal cord dysfunction syndrome)
- Shock (septic, cardiogenic, hypovolemic)
- Hereditary angioedema
- Medication toxicity/overdose
- Carcinoid syndrome (flushing syndromes)
- Systemic mastocytosis

# Triggers of anaphylaxis

#### Most Common

- Foods (up to 80% of reactions in kids)
- Stinging insect venoms
- Medications (B-lactams, NSAIDS)

#### **Examples of Less Common:**

- Natural rubber latex
- Exercise, +/- food associated
- Aeroallergens
- Mastocytosis
- Idiopathic
- Occupational allergens
- Seminal fluids
- Others ...



### Laboratory tests in the diagnosis of anaphylaxis



## Management of acute anaphylaxis

- α-adrenergic: \*vasoconstriction\*
  - increase peripheral vascular resistance, reversing peripheral vasodilation (35% blood volume may be lost in first 10min)
  - Relieves airway obstruction from mucosal edema
  - decreasing urticaria and angioedema
- β1 effects:
  - chronotropic and inotropic effects on heart
- β2 effects:
  - bronchodilation
  - reduction of inflammatory mediator release from mast cells and basophils (including PAF).

## Epinephrine: ? evidence

Based on observational studies, animal models, retrospective and epidemiologic studies, and fatality studies

-delays are associated with fatality, severe morbidity, biphasic reactions





# Epinephrine- give early!

- Epinephrine is the drug of choice for anaphylaxis
  - available in auto-injectors which are simple to use and give reliable results
  - reverses associated hypotension and bronchospasm
- Fatality rates are highest in patients in whom treatment with epinephrine is delayed
  - increased risk of hospitalization and poor outcomes, including hypoxic-ischemic encephalopathy and death.
- There are no absolute contraindications to epinephrine administration in the setting of anaphylaxis

O'Dowd SC, et al. Anaphylaxis in Adults. Available at: www.uptodate.com 2006.

Fleming JT, Clark S, Camargo CA Jr, Rudders SA. Early treatment of food induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. J Allergy Clin Imm Pract. 2015;.

Sicherer SH, et al. JACI 2005; 115(3):575-83.

Ellis et al. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. Ann Allergy Asthma Immunol 2007 Mehr et al. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy 2009

## Epinephrine: Dose and Route

- IM route: mid-anterolateral thigh
- 0.01 mg/kg of 1:1000
  - Maximum 0.5 mg (adults)
  - 0.3mg (children)
- Dose can be repeated q5-15 minutes PRN
- If shock imminent or has already developed
  - Epi by slow IV infusion
  - titrate dose to non-invasive continuous monitoring

## Anaphylaxis management

- Avoid sudden position changes
- Elevate lower extremities
  - Preserve circulating fluid in vascular compartment
  - Avoid empty vena cava/empty ventricle syndrome
- Supplemental O<sub>2</sub> to all pts with respiratory distress, or receiving repeated Epi
  - Consider for pts with concomitant asthma, COPD, CV disease
- Intravascular fluid
  - Titrate rate to BP, HR and function, u/o

## 2nd Line Medications

#### • Antihistamines

- Relieve skin, nasal and ocular symptoms
- Do not prevent or relieve upper airway obst/shock
- Recent Cochrane analysis found no trials to support their use
- Development of somnolence can interfere with patient assessment
- <u>Opportunity for further investigation</u>

#### Corticosteroids

- Onset of action takes several hours
- May potentially relieve protracted and prevent biphasic anaphylaxis, these effects have never been proven
- Opportunity for further investigation

#### Bronchodilators

• <u>Adjunctive</u> medication for bronchospasm in addition to epinephrine

## Treatment of refractory anaphylaxis

- Minority of patients
- IV vasopressors
  - No clear superiority of dopamine, dobutamine, NE, phenylephrine, or vasopressin (added to epi alone, or compared with one another)

Mullner et al. Vasopressors for shock. Cochrane Database Syst Rev. 2004 Ellender et al. The use of vasopressors and inotropes in the emergency medical treatment of shock. Emerg Med Clin North Am. 2008 Gueugniaud et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. NEJM 2008



Simons et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. JACI 2011



Simons et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. JACI 2011


#### What is the Clinical Course of Anaphylaxis?



### Duration of monitoring

- Moderate Resp/CV compromise
  - Monitor 4-6 hours min
- Severe
  - Monitor 10-12 hrs  $\rightarrow$  days
- Biphasic reactions
  - Up to 23% adults
  - up to 11% children

Smit et al. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. J Emerg Med. 2005

Ellis AK et al. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. Ann Allergy Asthma Immunol. 2007

Mehr et al. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy. 2009 Scranton et al. Incidence and characteristics of biphasic reactions after allergen immunotherapy. JACI 2009

Confino-Cohen et al. Allergen immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective

study. Ann Allergy Asthma Immunol. 2010

A parent (with a newly diagnosed food allergic child)...

- A 3-year-old known asthmatic had a reaction following ingestion of peanut butter.
- While helping to prepare for her birthday party, he suddenly developed facial swelling, and an itchy red bumpy rash all over, became wheezy and short of breath, and vomited en route to the hospital
- He was treated in the ER and now is with his parents in your office.



#### Parent:

"Doc, It seems like there's more allergic reactions now than when I

was a kid...is this true?"

Your correct response is...

A. Yes, food reactions have become much more common

B. No, people are now just more likely to blame food allergies for their problems

C. Both A and B are correct.

### Prevalence of Anaphylaxis

- True prevalence of anaphylaxis is likely underestimated and underreported <sup>1,2</sup>
  - Is increasing and in the range of 0.05% to 2%
  - Highest number of cases is in children and adolescents.<sup>2-4</sup>
- Canadian studies have reported anaphylaxis risk rates of 0.50% to 0.95%<sup>1</sup>
- Anaphylaxis is common, with an estimated prevalence in the general population of at least 1.6%<sup>4</sup>

1. Ben-Shoshan & Clarke. Allergy 2011;66:1-14 2. Lee & Vadas. Clinical & Experimental Allergy, 2011

3. Kim & Fischer. Allergy, Asthma & Clinical Immunology 2011;7(Suppl 1):S6. 4. Lin et al. Ann Allergy Asthma Immunol. 2008

4.Wood, Camargo, Sampson et al. JACI 2014

Rate of visits for anaphylaxis a small but growing proportion (increasing by 95%)



Sept, 2015. Canadian Institute for Health Information (CIHI) released statistics on allergy and anaphylactic reactions requiring ER visits from 2007-2014.

**Good news...low fatality rates** Fatal anaphylaxis in the US, 1999-2010 Elina Jerschow, MD JACI August 2014

- 2458 fatal anaphylaxis cases of all causes, with an overall incidence of 0.69 persons per million/year.
- Medication reactions (58.8%)
  - unspecified anaphylaxis (19.3%)
    - venom-induced anaphylaxis (15.2%)
      - food-induced anaphylaxis (164 fatalities, 6.7%)
- Significant increase in fatal drug-induced anaphylaxis over 12 years
- Fatal anaphylaxis caused by medications, food, and unspecified allergens was significantly associated with African American race and older age



# Fatal food-induced anaphylaxis was significantly associated with age



#### Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012

Paul J. Turner, FRACP, PhD,<sup>a,b</sup> M. Hazel Gowland, BA,<sup>c</sup> Vibha Sharma, FRCPCH,<sup>d</sup> Despo lerodiakonou, MD, PhD,<sup>a</sup> Nigel Harper, FRCA,<sup>d</sup> Tomaz Garcez, MRCP, FRCPath,<sup>d</sup> Richard Pumphrey, FRCPath,<sup>d</sup> and Robert J. Boyle, MBChB, PhD<sup>a</sup> London, Farnborough, and Manchester, United Kingdom, and Sydney, Australia

- Location: England and Wales
- Time period: 21-year period (1992-2012)
- What was studied:
  - anaphylaxis related hospital admissions and fatalities
  - time trends
  - age and sex distribution

#### Turner et al. 2015: Results

- Admissions due to anaphylaxis increased from 1992 until 2008 when the rate plateaued
- The increase was from 1.0 to 7.0 cases per 100,000 population per annum
- Same trend regardless of gender.
- No relation to ICD changes or 4-hr wait target in ED



#### Turner et al. 2015: Food-induced anaphylaxis

 Admissions increased between 1998 and 2012. Increase of 106% (P < .0001)</li>



## Peanut allergy in children in the U.S. continues to rise...



#### The scope of the problem...

- Recent estimates suggest 4% of total population have food allergy
- Higher prevalence in children (Branum. Food allergy among children in the United States. Pediatrics 2009)
  - 6% by 3 years based on food challenges and convincing clinical history
  - 18% increase between 1997 and 2007

- 1. Prevalence of food allergies: a metanalysis Rona RJ JACI 2007
- 2. Prev and cumulative incidence of food hypersensitivity in the first 3 years of life *Venter CAllergy 2008*
- 3. Sicherer JACI 2003; Grundy JACI 2002; Hourihane JACI 2007 (gov impact study)
- 4. Gupta et al Prevalence, severity, and distribution of childhood food allergy in the US Pediatrics, 2011

#### The scope of the problem...

• 8% of U.S. Children have a food allergy



Prevalence, severity, and distribution of childhood food allergy in the US. Gupta et al Pediatrics, 2011

#### Prevalence of Food Allergies

Food	Young Children	Adults
Milk	2.5%	0.3%
Egg	1.3%	0.2%
Peanut	1.5%	0.6%
Tree nuts	0.2%	0.5%
Fish	0.1%	0.4%
Shellfish	0.1%	2.0%
Sesame seed	.2%	.05%
Overall	<b>6%</b>	4%

### Turner et al. 2015: Results

- Fatality rates from anaphylaxis remained stable
- Mean rate of 0.047 cases (95% CI, 0.042-0.052 cases) per 100,000 population per year
- No increase in fatalities (estimated rate ratio, 1.00; 95% CI, 0.98-1.01; P > 0.05)
- No difference by gender.



Anaphylaxis prevalence and mortality rates

#### So you kindly summarize to the parent....

- Food allergy rates are increasing- prevalence now between 4-8%
- ER visits for allergic reactions and especially anaphylaxis rates are increasing- Prevalence rates as high as 2%
- Mortality is extremely low (<0.5% in those hospitalized or receiving ER treatment for anaphylaxis), and does not appear to be increasing despite increasing rates of anaphylaxis
  - We're doing something right?!
- Cardiovascular morbidity, older age, uncontrolled asthma are risk factors
  - Refs:
  - 1. Fatal anaphylaxis: Mortality rate and risk factors. Turner et al JACI 2017
  - 2. Anaphylaxis. Fischer et al. Allergy Asthma Clin Immunol 2018

Parent: (now looking at her watch [ie smart phone] realizing she still has lots of questions about her own child!)

"Wow, that's impressive, thanks for all the info doc!...but for my daughter, when do I use her Epipen?...do I really have to use it right away or can it wait until I arrive at the ER? Or won't Benadryl work as well if I give it first? Do I need more than one Epipen? After biting into a cookie the child cries out, "my tongue is sore".

- Lips are swollen.
- Voice is hoarse.

# What does the typical parent do first?



The Children's Allergy & Asthma Education Centre 2014 ©

"What if she doesn't need the Epi-pen? What would happen then?" "Maybe I'll wait...maybe she'll get better...her breathing is fine...if she gets worse the hospital IS pretty close...WAIT... we have Benadryl, I'll use THAT!

#### Risk factors for more severe anaphylaxis

- <u>Delayed administration of Epi-Pen during acute</u> <u>reaction/ failure to carry epinephrine</u>
- History of previous severe reaction to a food
  - Yearly annual recurrence rate of 18% in children<sup>1</sup>
- Co-existent asthma (esp. if poorly controlled)
- Denial or minimization of symptoms
- Failure to inquire about food ingredients
- Lack of awareness by others
- Beta-blocker and ACE inhibitor therapy
- Other chronic disease: cardiovascular, psychiatric, mastocytosis
- Cofactors: Exercise and acute infection

Ref: The Risk of Recurrent Anaphylaxis. O'Keefe A, Clarke A, Ben-Shoshan M J Pediatr. 2017

I NOW HAVE AN EPIPEN. MY FRIEND GAVE IT TO ME AS HE WAS DYING.

TO HIM THAT I HAVE IT.

#### Reasons why the epinephrine was NOT given...

- waited to see if the child will get better on their own
- used antihistamines or puffer instead "Benadryl given at the ER"
- previous reaction didn't require epin of cine
- fear of doing harm if it isn't really media
- her breathing still seemed fire
- didn't have EpiPen with them
- not sure how or where b give epinephrine
- didn't want to go to hospital
- the hospital was very close...
- the hospital was too far away...









Delayed administration of epinephrine during acute reaction

- Benadryl provides an "out" when these factors are in play ("at least I'm doing something" or "its what the ER does")
- Need to distinguish between hosp vs community treatment
- Lack of understanding of the importance of <u>early</u> use



www.alamy.com - EMHMGM



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Reasons why we didn't use the autoinjector...

• When asked if the epinephrine could be given orally/SL (if this were available) would you have given it???

- Most reasons...secondary reasons reflecting FEAR of the autoinjector!
- Fear Denial and excuses...... Why??

Why such fear? Its a needle, of course! But there's more...

We as physicians have counseled our patients/families:

- "IF YOU USE YOUR AUTOINJECTOR, YOU NEED TO GO TO A HOSPITAL IMMEDIATELY"
- What's the message that the patient/family is hearing?
  - "This medication is DANGEROUS!"

### Case

- While in Mexico, a 14 year old girl (with known peanut allergy) was on a bus tour with Dad. She ate a candy bar with a Spanish label translated by someone who assured there were no peanuts.
- However, soon after ingestion, she developed obvious tongue swelling and throat tightening.
- 5 doses of Benadryl were given. Why??
- Dad, who was with her, stated that " I didn't think she should use it, as the nearest hospital was >2 hours away"!!

#### Case: 14 year old girl with peanut/tree nut allergy

"I'd rather die than use the Epi-Pen!"

- Met with parents, and after some discussion, the family agreed to return to the clinic with a recently expired Epi-Pen
- She was guided, through tears, to inject herself
- Her response? "That's it??" 😳



Parent (feeling quite relaxed now that child has fallen asleep in your office):

"Oh, doc, the junior autoinjector you prescribed has a dose of 0.15mg, would that too much for my daughter? She only weighs 8kg".

# CSACI position statement: epinephrine auto-injectors and children < 15 kg

Michelle Halbrich<sup>1\*</sup>, Douglas P. Mack<sup>2</sup>, Stuart Carr<sup>3</sup>, Wade Watson<sup>4</sup> and Harold Kim<sup>5,6</sup> 2015

- Fatal anaphylaxis r/t delayed use of epinephrine
- Supports the use of 0.15mg epi autoinjector for a child at risk for anaphylaxis
- Adverse effects in children <15kg expected to be mild and transient
- Much greater risk of not receiving epi, which could include fatality

#### AMERICAN ACADEMY OF PEDIATRICS CLINICAL REPORT: Pediatrics 2015 Guidance for the Clinician in Rendering Pediatric Care

**Epinephrine for First-Aid Management of Anaphylaxis** 

Scott H. Sicherer, MD, FAAP, F. Estelle R. Simons, MD, FAAP, and the Section on Allergy and Immunology

"International guidelines suggest that when using EAIs, patients weighing 7.5 to 25 kg should receive the 0.15-mg dose" (average weight of a 5-6-month-old) Treatment of allergy and anaphylaxis: Avoidance, epinephrine...anything else?



"Bit of a bummer really, you've got a nut allergy"

## Food Allergy Immunotherapy

- Oral IT (OIT)
  - swallowed with food
- Sublingual IT (SLIT)
  - sublingually then swallowed
- Epicutaneous ("patch")
- <u>Differences</u>
  - amount of protein, route?, digestion?, possibility of causing tolerance?





SLIT



Epicutaneous

