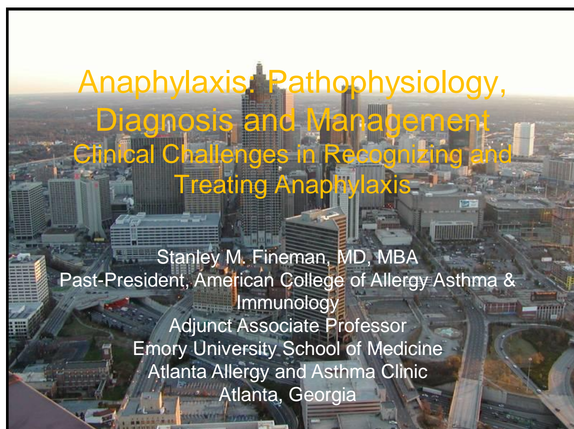


Disclosures

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

- -Research support: Sunovion, Genetech, Shionogi
- -Speakers Bureau: AstraZeneca, Genetech/Novartis

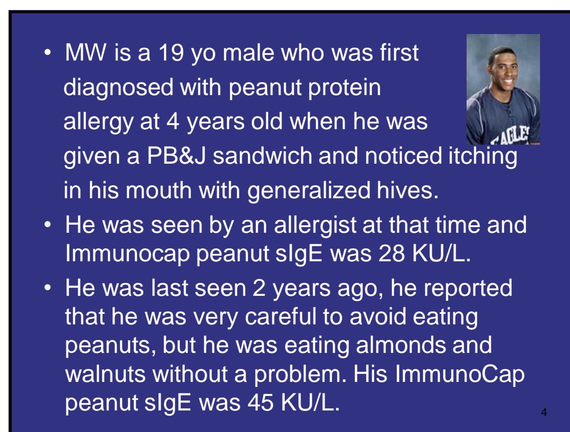
2

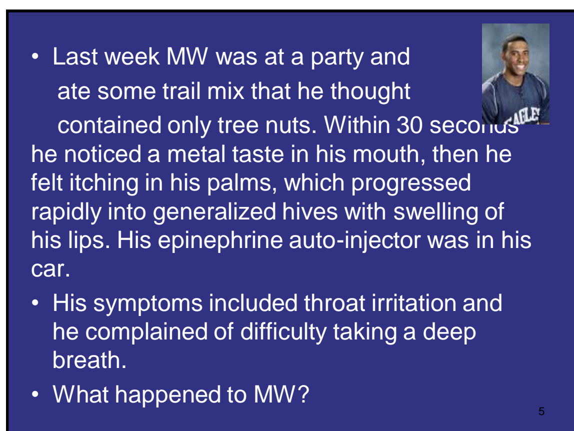
Learning Objectives

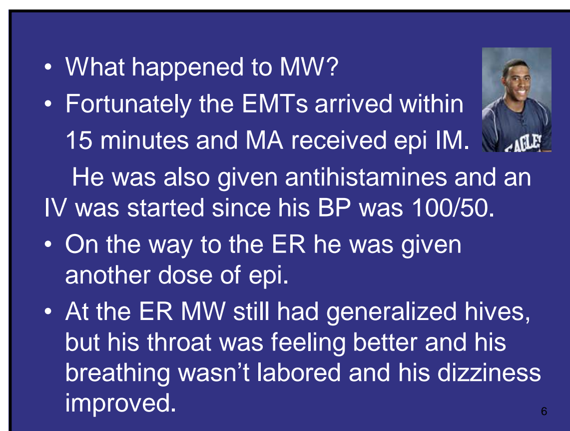
At the conclusion of the presentation, the attendees should be able to discuss the following:

- Recognize the most common triggers of anaphylaxis
- Understand how anaphylaxis presents to emergency departments
- Learn how to be prepared in a medical office to handle patients with anaphylaxis

3







Questions about Anaphylaxis:

- What is the definition of anaphylaxis?
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- What are the most common signs & symptoms of anaphylaxis?
- Can we predict severity of subsequent anaphylaxis episodes?

7

8

"The discovery of anaphylaxis is not at all the result of deep thinking, but of simple observation, almost accidental…"

C Richet, 1913.

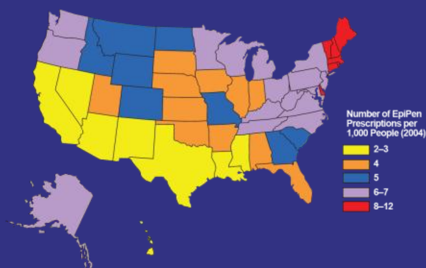
Epidemiology of Anaphylaxis

- 1-15% of US population (2.8 to 42.7 million people) may be at risk (Yocum et al, Neugut et al)
  - 30/100,000 population/year (Yocum et al)
- Estimated annual incidence
  - 21/100,000 (Yocum et al)
- 0.95% of 1.2 million individuals in a claims database were dispensed injectable epinephrine
  - Rates ranged from 1.44% of patients <17 years old to 0.32% of patients >65 years
- Incidence of anaphylaxis is increasing

Sheikh et al, BMJ, 2000; Yocum et al, *J Allergy Clin Immunol*, 1999; Simons et al, *J Allergy Clin Immunol*, 2002, Neugut et al, *Arch Int Med*, 2001.

Prevalence Data May Come From Epinephrine Auto-injector Prescriptions

Regional Differences in Epinephrine Auto-injector Usage



Camargo CA, et al. *J Allergy Clin Immunol.* 2007;120:131-136.

11

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12

Definition of Anaphylaxis:

Clinical Criteria for Diagnosing Anaphylaxis

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm)
- Reduced BP or associated symptoms of end-organ dysfunction

NIAID, National Institute of Allergy and Infectious Disease; FAAN, Food Allergy and Anaphylaxis Network; BP, blood pressure; SBP, systolic blood pressure.
*Low SBP for children is defined as <70 mm Hg from 1 month to 1 year, <70 mm Hg plus [2x age] from 1 to 10 years, and <90 mm Hg from 11 to 17 years.
Sampson HA, et al. *Ann Emerg Med.* 2006;47:373-380, *Second Symposium on the Definition and Management of Anaphylaxis: J Allergy Clin Immunol 2006;117:391-7*

13

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OR

≥2 of the following that occur rapidly after exposure to a *likely* allergen (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise
c. Reduced BP or associated symptoms
d. Persistent gastrointestinal symptoms (eg, cramping, abdominal pain, vomiting)

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b. Respiratory compromise
c. Reduced BP or associated symptoms
d. Persistent gastrointestinal symptoms (eg, cramping, abdominal pain, vomiting)

OR

Reduced BP after exposure to *known* allergen (minutes to several hours):

a. Infants and children: low SBP (age specific) or >30% decrease in SBP*
b. Adults: SBP of <90 mm Hg or >30% decrease from that person's baseline

NIAID, National Institute of Allergy and Infectious Disease; FAAN, Food Allergy and Anaphylaxis Network; BP, blood pressure; SBP, systolic blood pressure.
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Patterns of Anaphylaxis

- Uniphasic
  - Symptoms resolve within hours of treatment
- Biphasic
  - Symptoms resolve after treatment but return between 1 and 72 hours later (usually 1-3 hours)
- Protracted
  - Symptoms do not resolve with treatment and may last >24 hours

Lieberman, 2004

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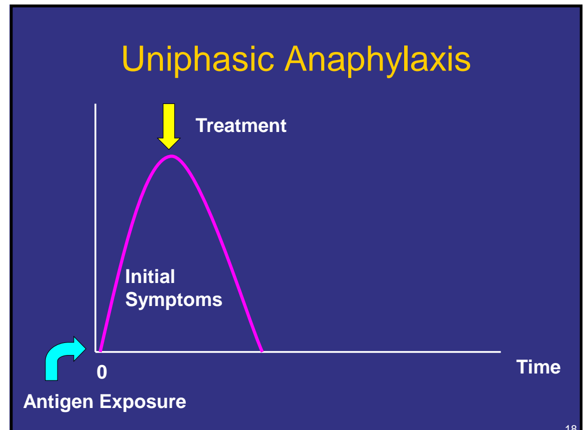

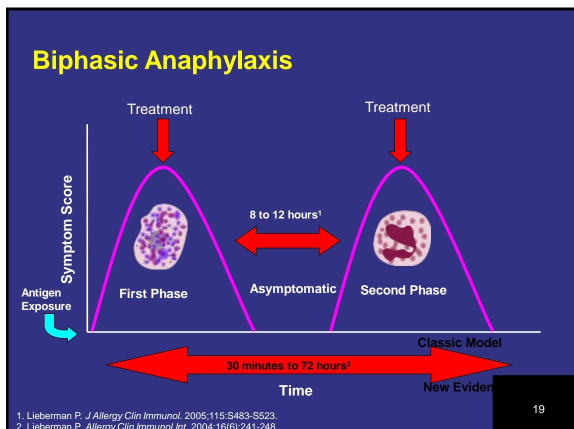

Biphasic Anaphylaxis

- Incidence reported: 16-36%
- Second response may be similar to, less severe of more severe than original episode
- Fatalities can occur, risk factors include:
  - Pt on β-blocker
  - Oral administration of antigen
  - Delay in onset of epinephrine administration
  - Presence of hypotension or laryngeal edema
  - Inadequate dose of epinephrine

Stark and Sullivan, *J Allergy Clin Immunol*, 1986; Lieberman, *Allergy Clin Immunol Int*, 2004; Ellis and Day, *Curr Allergy Asthma* Rep, 2003

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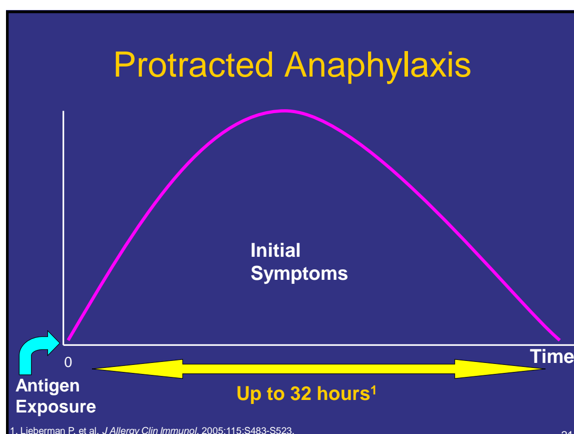

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Frequency and Occurrence of Signs and Symptoms of Anaphylaxis

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
Hypotension, dizziness, syncope, diaphoresis	30-35
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25-30
Miscellaneous	
Headache	5-8
Substernal pain	4-6
Seizure	1-2
Angor animi (sense of impending doom)	—

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

In Adults, Most Cases Are Idiopathic and Females Predominate

- N = 601 cases
- 62% of cases were female
- 37% were atopic by history confirmed with skin test

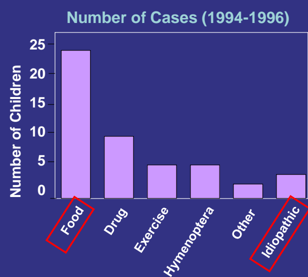
Exercise 5%
Other, 3%
Medication 11%
Idiopathic, 59%
Food, 22%

24

Webb LM, Lieberman P. *Ann Allergy Asthma Immunol*. 2006;97(1):39-43.

In Children, Most Cases Are Food-related and Males Predominate

- N = 46 cases (28 male, 18 female)
- Median age at 1st episode: 5.8 years
- Only small proportion idiopathic



Cianferoni A, et al. *Ann Allergy Asthma Immunol.* 2004;92:464-468.

25

Anaphylaxis in a New York City pediatric emergency department: Triggers, treatments, and outcomes

Faith Huang, MD, Kanwaljit Chawla, MD, Kirsi M. Järvinen, MD, PhD, and Anna Nowak-Węgrzyn, MD *New York, NY*

213 reactions in 192 children (97 males) 2004-2008
Foods 71%, Drugs 9%, unknown 15%

28 (14%) hospitalized
2 doses of epi in 13 (6%)
of those 9 (69%) were hospitalized
Those getting epi prior to arrival at PED lower rate of hosp (25%) vs 89% in those getting 2nd dose of epi in PED

J Allergy Clin Immunol 2012;129:162-8

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Faith Huang, MD, Kanwaljit Chawla, MD, Kirsi M. Järvinen, MD, PhD, and Anna Nowak-Węgrzyn, MD *New York, NY*

Conclusions:
Food is main trigger
Tx with 2 doses of epi is assoc ↑hosp
Tx with epi prior to PED assoc ↓hosp
Medicaid less likely to receive epi prior to PED

J Allergy Clin Immunol 2012;129:162-8

27

Anaphylaxis in emergency department patients 50 or 65 years or older

Ronna L. Campbell, MD, PhD*; John B. Hagan, MD†; James T. C. Li, MD, PhD†; Samuel C. Vukov*; Abhijit R. Kanthala, MBBS*; Vernon D. Smith, MD*; Veena Manivannan, MBBS*; M. Fernanda Bellolio, MD*; and Wyatt W. Decker, MD*

- 220 pts in ED, 4/2008-6/2010
- Medications 24% of pts >50yo
- Food most cmn (42%) in pts <50yo
- Food cause in 14% of >50yo
- >65yo more likely to have hypotension

Ann Allergy Asthma Immunol 2011;106:401-406

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Conclusions:
- Decreased likelihood of food trigger
- Increased likelihood of CV symptoms
- Decreased likelihood of going home from ED
- Decreased likelihood of Rx for SI-epi

Ann Allergy Asthma Immunol 2011;106:401-406

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A population-based epidemiologic study of emergency department visits for anaphylaxis in Florida

Laurel Harduar-Morano, MPH,[a] Michael R. Simon, MD,[b] Sharon Watkins, PhD,[a] and Carina Blackmore, DVM, PhD[a] *Tallahassee, Fla, and Royal Oak and Detroit, Mich*

- N=2751, 2005-2006
- Young male (0-4yo) 8.2/100K
- Adult female (15-54yo) 9.9/100K
- Trigger identified in 37%
  - Food 49%
  - Insect stings 29%
  - Medications 22%

J Allergy Clin Immunol 2011;128:594-600

30

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Tallahassee, Fla, and Royal Oak and Detroit, Mich

Conclusions:

- Relatively lower rate of anaphylaxis
- Children more likely food induced
- Males more likely venom, or medications
- Venom most cmn in Aug, Sept & Oct.
- Children less likely to have medication trigger compared to older pts

J Allergy Clin Immunol 2011;128:594-600 31

Anaphylaxis with SCIT

- Systemic reactions 0.25-1.3%
- Fatal reactions 1 in 2.5 million injections
- Near-fatal anaphylactic reactions 1 in 1 million injections
- Predisposing factors
  - Uncontrolled asthma
  - Repeated large local reactions

Lockey RF et al. J Allergy Clin Immunol 1987;79:660-77
Reid MJ, et al. J Allergy Clin Immunol 1993;92:6-15.
Lockey RF, et al. Ann Allergy Asthma Immunol 2001;87:47-55.
Bernstein DI, et al. J Allergy Clin Immunol 2004;113:1129-36.

32

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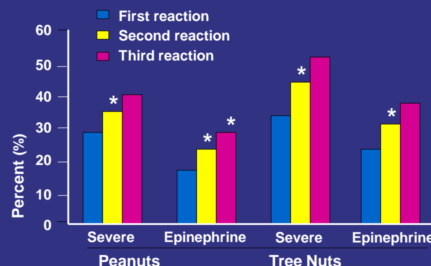
A Higher Proportion of Subsequent Reactions Are Severe



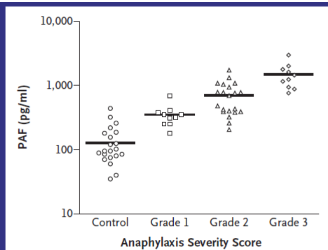
*Indicates a reaction significantly greater than prior reaction ($P<.05$).
Data from the first 5,149 patients in a voluntary registry for peanut and tree nut allergy.

Sicherer SH, et al. *J Allergy Clin Immunol.* 2001;108:128-132.

34

Platelet-Activating Factor, PAF Acetylhydrolase, and Severe Anaphylaxis

Peter Vadas, M.D., Ph.D., Milton Gold, M.D., Boris Perelman, Ph.D., Gary M. Liss, M.D., Gideon Lack, M.D., Thomas Blyth, M.D., F. Estelle R. Simons, M.D., Keith J. Simons, Ph.D., Dan Cass, M.D., and Jupiter Yeung, Ph.D.



N Engl J Med 2008;358:28-35 35

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Conclusions:

- Circulating PAF is increased and PAF acetylhydrolase activity is decreased in proportion to the severity of organ system involvement in patients with acute allergic reactions.
- PAF acetylhydrolase was significantly lower in patients with fatal peanut anaphylaxis compared to those with milder reactions or controls.

N Engl J Med 2008;358:28-35 36

What are Predisposing factors?

CONCOMITANT DISEASES*

Asthma and other respiratory diseases | Cardiovascular diseases | Mastocytosis/clonal mast cell disorders | Allergic rhinitis and eczema** | Psychiatric illness (e.g. depression)

CONCURRENT MEDICATIONS/ETHANOL/RECREATIONAL DRUG USE*

β-adrenergic blockers and ACE inhibitors*** | Ethanol/sedatives/hypnotics/antidepressants/recreational drugs (potentially affect recognition of anaphylaxis triggers and symptoms)

CO-FACTORS THAT AMPLIFY ANAPHYLAXIS*

Exercise | Acute infection (e.g. a cold or fever) | Emotional stress | Disruption of routine (e.g. travel) | Premenstrual status (females)

Simmons FER, et al. J Allergy Clin Immunol 2011;127:587-93

37

Fatal Anaphylactic Reactions Are Often Associated With:

- Delay between time of symptom onset and administration of treatment
- History of asthma
- Adverse therapeutic event
- However, most fatal reactions are unpredictable

38

Pumphrey, *Curr Opin Allergy Clin Immunol 2004;* Sampson et al, *N Engl J Med, 1992;* Pumphrey, *Clin Exp Allergy, 2000*

Lack of Awareness Contributes to Inadequate Treatment

- Physicians often fail to diagnose anaphylaxis correctly
  - Can be confused with other conditions
    - Septic or other types of shock
    - Asthma
    - Airway obstruction with foreign body
    - Panic attacks
  - Failure to plan future management
- Lack of education contributes to low levels of physician awareness
- Inadequate knowledge of epinephrine and its use

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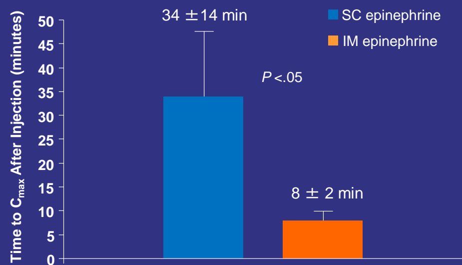
Tang AW. *Am Fam Physician* 2003

Why IM Epinephrine? Absorption of Epinephrine Faster With IM vs SC Injection

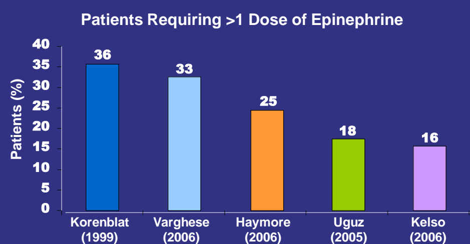


SC, subcutaneous; C_{max}, maximum concentration.

Adapted from Simons FER, et al. *J Allergy Clin Immunol.* 2004;113:837-844.

40

Frequency of Need for 2 Doses of Epinephrine for Anaphylaxis



Korenblat P, et al. *Allergy Asthma Proc.* 1999;20:383-386;
Varghese M, Lieberman P. *J Allergy Clin Immunol.* 2006;117(2, suppl):S305. Abstract 1178;
Haymore BR, et al. *Allergy Asthma Proc.* 2005;26(5):361-365;
Uguz A, et al. *Clin Exp Allergy.* 2005;35:746-750;
Kelso JM. *J Allergy Clin Immunol.* 2006;117(2):464-465.

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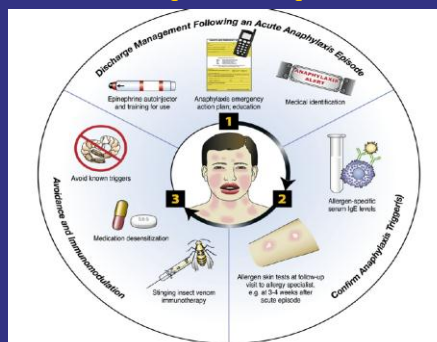
Discharge management



Simmons FER, et al. J Allergy Clin Immunol 2011;127:587-93.

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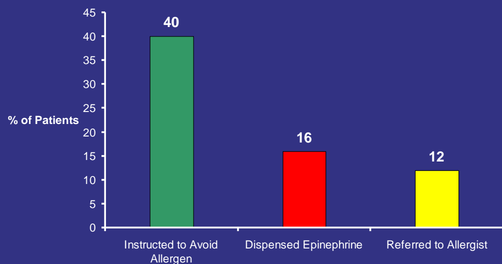
Inadequate Management Post ER for Food Anaphylaxis

21 ED over 12 months



Clark et al, *J Allergy Clin Immunol*, 2004

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Recommended Office Management

- Prompt recognition
- Epinephrine and oxygen are 'most important' therapeutic agents.
- Appropriate volume replacement
- Medical facilities should have an established action plan in place
- Physicians and office staff should maintain clinical proficiency in anaphylaxis management.

44 J Allergy Clin Immunol 2010;126:477-80.

Anaphylaxis Conclusions

- Anaphylaxis is a life-threatening acute reaction which is under-reported, frequently misdiagnosed, and under-treated
  - More common than previously thought
- Rapid and proper administration of epinephrine is the standard of treatment
  - Many patients require a second epinephrine injection to treat anaphylaxis
- Patient education needed – delays in treatment, improper administration and outdated epinephrine
- Physicians fail to properly diagnose and treat anaphylaxis – especially in the ED

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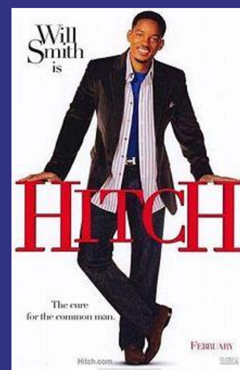

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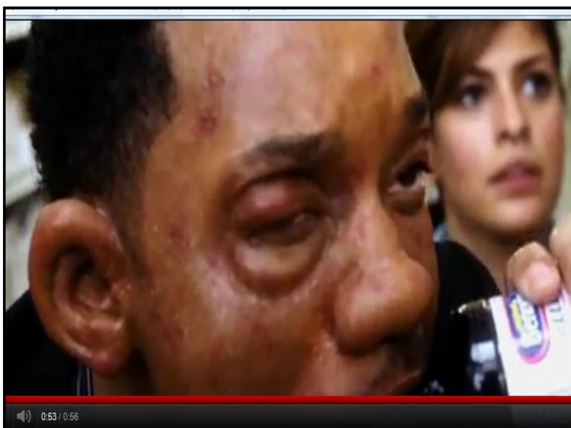

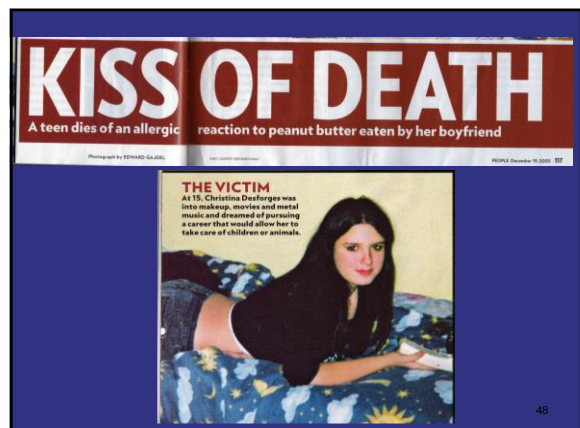

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Anaphylaxis Action Plan

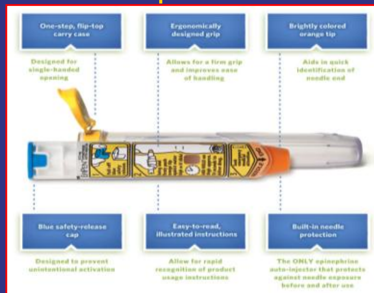
Available at: www.acaai.org or www.aanma.org

Anaphylaxis Action Plan

Available at: www.foodallergy.org/files/FAAP.pdf

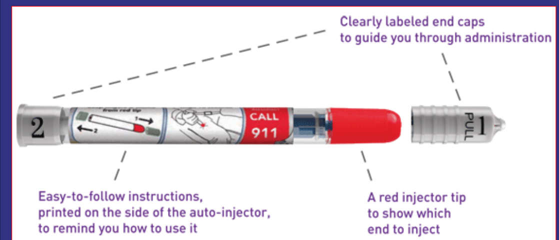
The Food Allergy Action Plan is available at: http://www.foodallergy.org/files/FAAP.pdf

Comparison of Auto-injectors: EpiPen



Available at: http://www.epipen.com/pdf/EPI_HowtoTearSheet.pdf.

Comparison of Auto-injectors: Adrenaclick



Available at: http://www.adrenaclick.com/about-adrenaclick/.

Comparison of Auto-injectors: Auvi-Q

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55