Adventures of Anaphylaxis: Diagnosis & Treatment

JANE PURSER, MD

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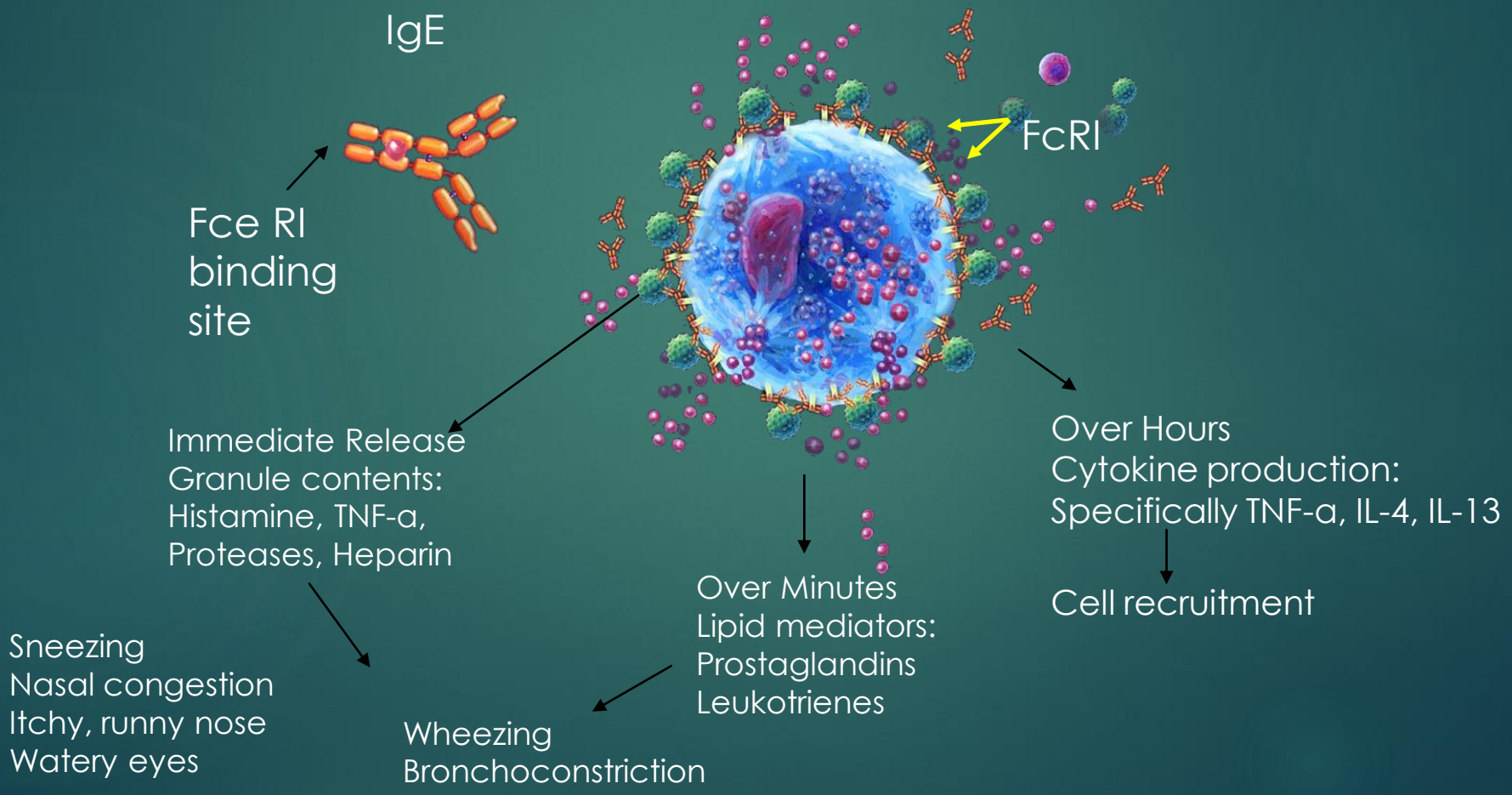
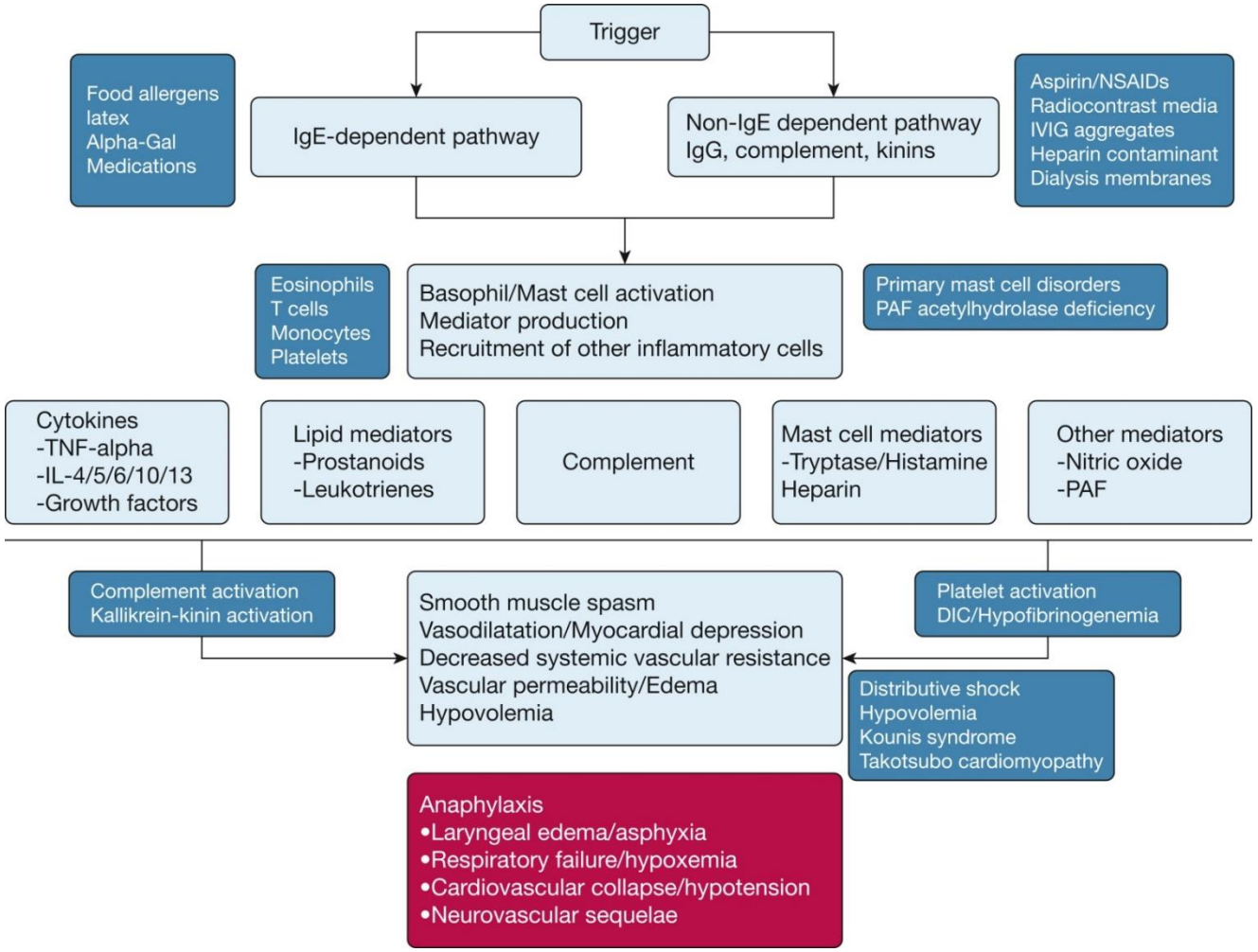
Objectives

- Recognize the broad spectrum of clinical presentations of anaphylaxis
- Review diagnostic measures available to diagnose
- Review common triggers of anaphylaxis
- Ensure the attendee can prescribe the appropriate medications for patients to have at home
- Review the spectrum of triggers of anaphylaxis and how they are investigated by the allergist

IgE-dependent Release of Inflammatory Mediators





Mechanisms underlying anaphylaxis-IgE and non-IgE-dependent pathway. DIC = disseminated intravascular coagulation; IVIG = intravenous immunoglobulin; NSAIDs = nonsteroidal anti-inflammatory drugs; PAF = platelet activating factor; TNF = tumor necrosis factor.

Anaphylaxis

- **A serious allergic reaction that is rapid in onset and may cause death**
- Clinical definition is based on expert consensus
  - Three scenarios are described in the next slide where anaphylaxis is likely
  - There is **allergen exposure** in second and third scenarios

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death*

▶* Manivannan V, Dekker W, Stead LG, Li J, Campbell R. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Int J Emer Med. 2009;2(1):3-5

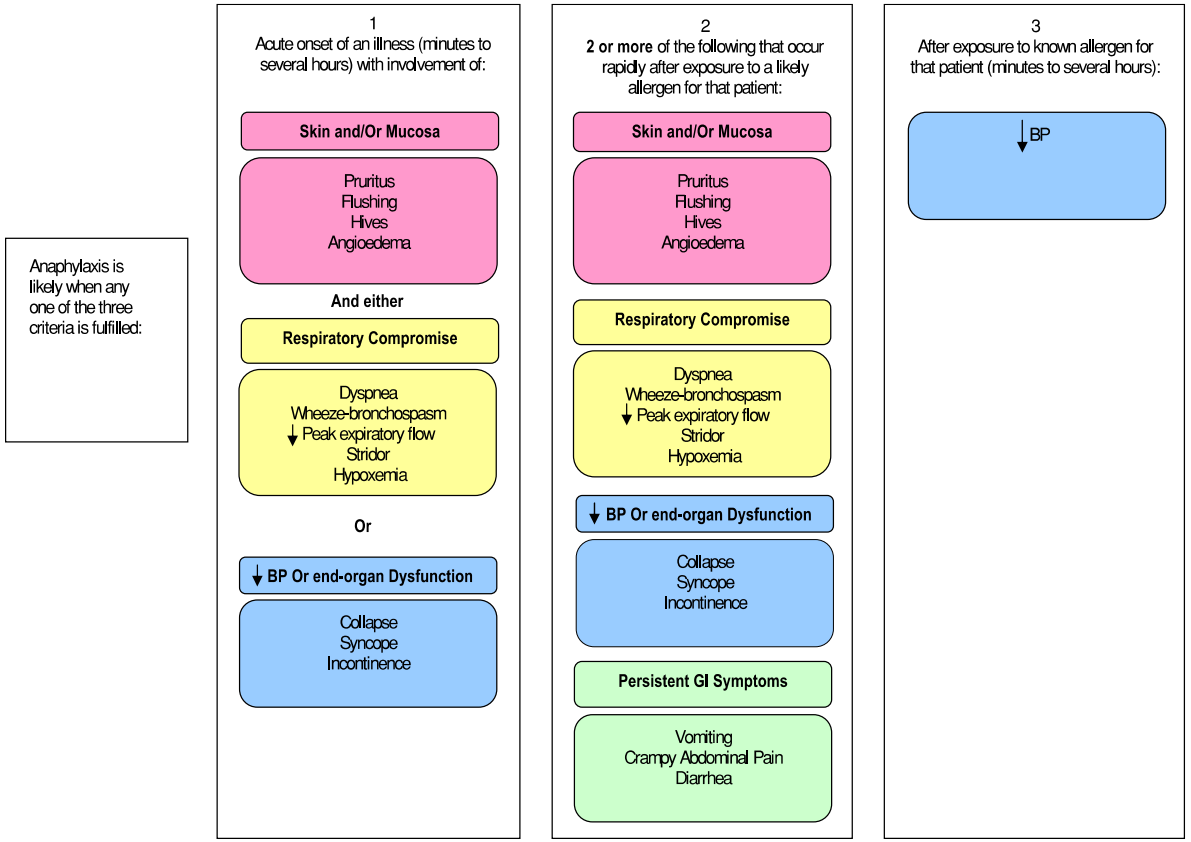


Fig. 1 Visual representation of the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis

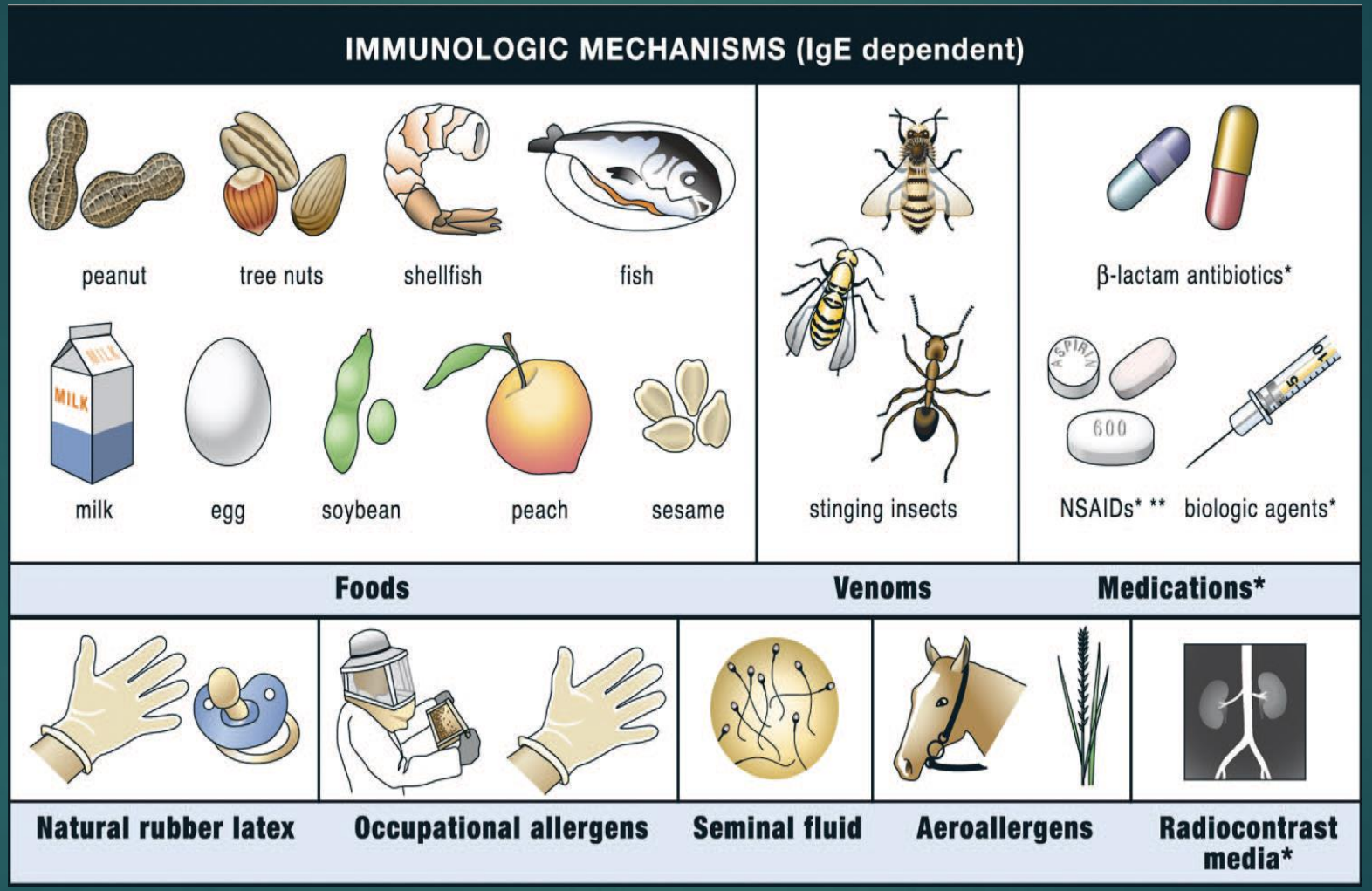
Epidemiology

- We do not know for sure how many are at risk
- National, cross-sectional survey based on self-report
  - 1.6 to 5.1% prevalence among adults in US
  - Most common triggers are medications (34%), foods (31%), and insect stings (20%)
    - Medications (34%)
    - Foods (31%)
    - Insect stings (20%)

Triggers of Anaphylaxis

- IgE-mediated
  - Medications
  - Foods
  - Insect venoms
  - Latex
  - Radiocontrast media (RCM)
- Non-IgE mediated and/or direct mast cell activation
  - RCM
  - Medications
  - Physical factors (exercise, cold, heat)
- Idiopathic

Anaphylaxis Triggers



Simons FER, Ardusso LRF, Bilo MB et. al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. WAO Journal 2011; 4:13-37 http://www.waojournal.org/content/4/2/13

Triggers of Anaphylaxis: Food

CHILDREN

- Eggs
- Peanuts
- Tree Nuts
- Seeds
- Wheat
- Soy
- Milk

ADULTS

- Peanuts
- Tree Nuts
- Seeds
- Fish
- Shellfish
- Red Meat

Simons FER, Ardusso LRF, Bilo MB et. al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. WAO Journal 2011; 4:13-37 http://www.waojournal.org/content/4/2/13

Triggers of Anaphylaxis: Insect Stings & Bites

- Bees
- Vespids
  - Yellow jackets, hornets, wasps
- Fire ants and other ants
- Scorpions
- Bites a far less common cause than stings

Simons FER, Ardusso LRF, Bilo MB et. al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. WAO Journal 2011; 4:13-37 http://www.waojournal.org/content/4/2/13

Iatrogenic Triggers of Anaphylaxis

- Diagnostic agents
  - RCM
- Medications
  - Antibiotics
  - Aspirin, NSAIDs
- Biological response modifiers
  - Anti-venoms
  - Monoclonal antibodies
- Blood transfusions
- Allergen immunotherapy

Joint Task Force on Practice Parameters: AAAAI, ACAAI, and JCAAI. J Allergy Clin Immunol 2005;115:S483-523

Triggers of Anaphylaxis: Latex

- Some groups are at increased risk
  - Healthcare workers
  - Children with spina bifida
  - Patients with multiple surgeries
- Increased incidence during the 1990's due largely to implementation of universal precautions
- Incidence has decreased since non-powder gloves and synthetic non-latex gloves have become available

Kelly KJ et al, J Allergy Clin Immunol 1994;93:813-6

Triggers of Anaphylaxis: Physical

- Exercise-induced
  - Food or medication are often co-factors
    - Wheat, celery, peanut and multiple others
    - May be more common than previously noted
- Physical urticaria may be caused by exposure to heat, cold, pressure, exercise and sunlight and vibration.
  - Most involve only the skin
  - Anaphylactic reactions occurring with physical urticaria are rare

Burgess B. EMedHome.com
https://www.aaaai.org/global/latest-research-summaries/New-Research-from-JACI-In-Practice/life-threatening-allergic-reaction

Signs & Symptoms

- Multiple organ systems potentially involved
  - Cutaneous: Flushing, pruritus, urticaria, angioedema
  - Gastrointestinal: Nausea, abdominal pain, vomiting, diarrhea
  - Respiratory: Upper or lower
    - Nasal pruritus, rhinorrhea, sneezing, throat tightness, dysphagia, shortness of breath, dyspnea, chest tightness, cough, wheeze
  - Cardiovascular: Faintness, hypotension, syncope, chest pain
  - Neurologic: Headache, blurred vision, seizure (rare), impending sense of doom
  - Genitourinary: Uterine cramping, loss of bladder control

Anaphylaxis - Patterns

- Uniphasic (most): typically peaks within 1 hour and resolves within hours
- Biphasic: recurrence of symptoms after apparent complete resolution, and without further exposure
  - Up to 8 hours later and rarely much later
  - Unknown incidence, from 1-23% in literature
  - Associations with increased severity of initial reaction, delayed epinephrine administration, fatal reactions
- Protracted/refractory: prolonged, with symptoms lasting days despite aggressive treatment

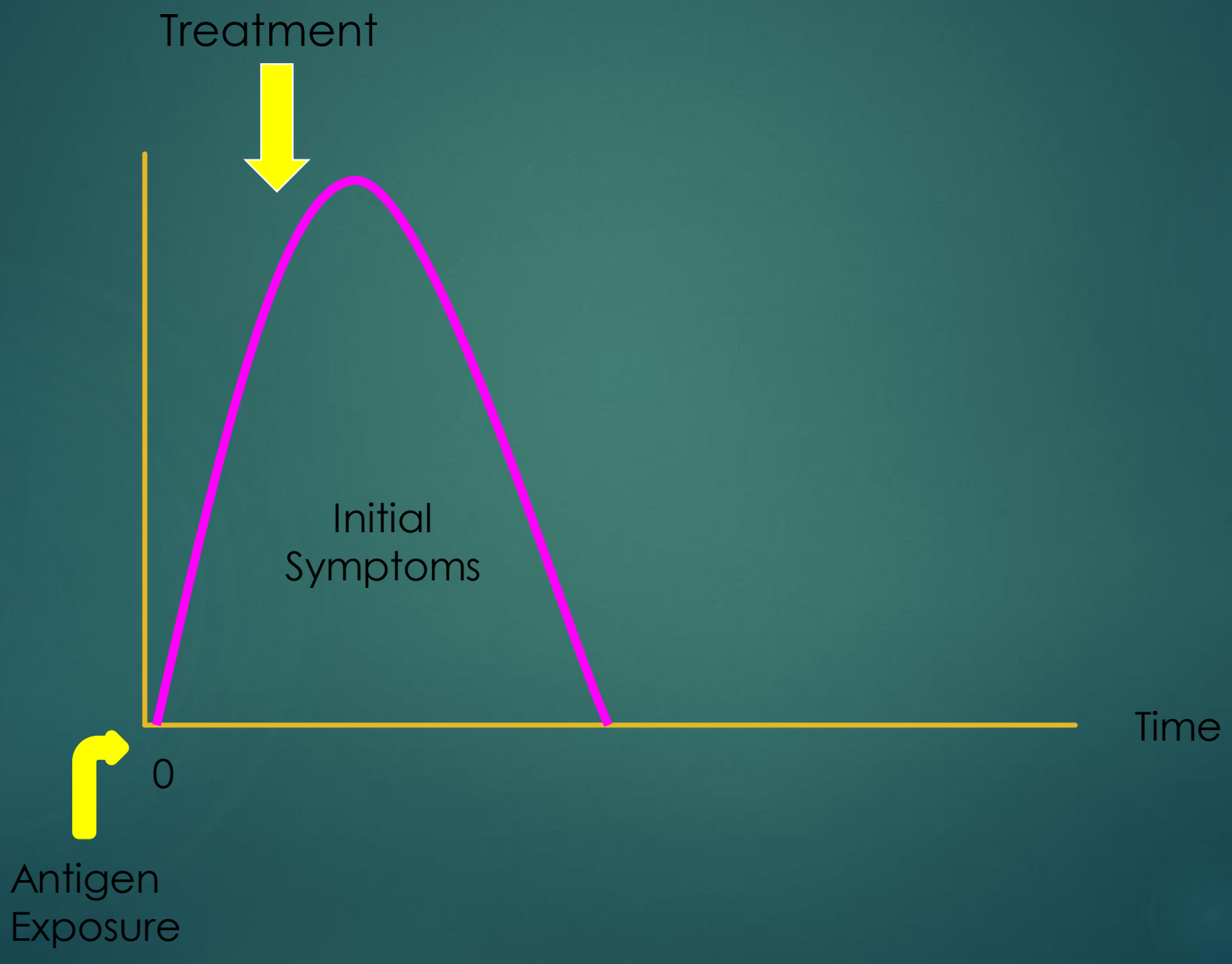
Lieberman P et al., J Allergy Clin Immunol 2010;126:477-80

Alqurashi W et al., Ann Allergy Asthma Immunol 2015;115:217-23

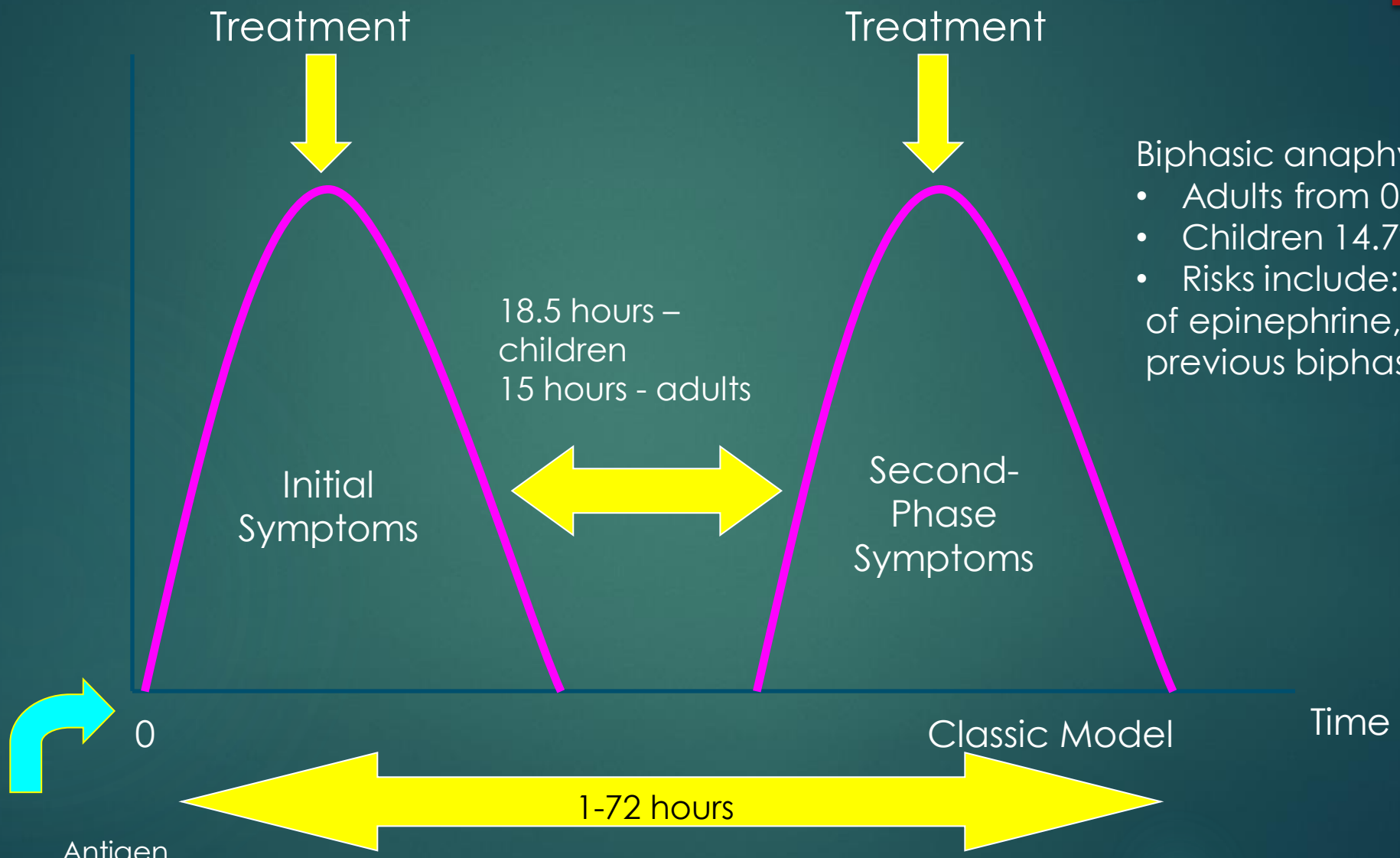
Ko BS et al., Ann Allergy Asthma Immunol 2015;115:312-16

Lee S et al., J Allergy Clin Immunol Pract 2015;3:408-16

Uniphasic Anaphylaxis



Biphasic Anaphylaxis

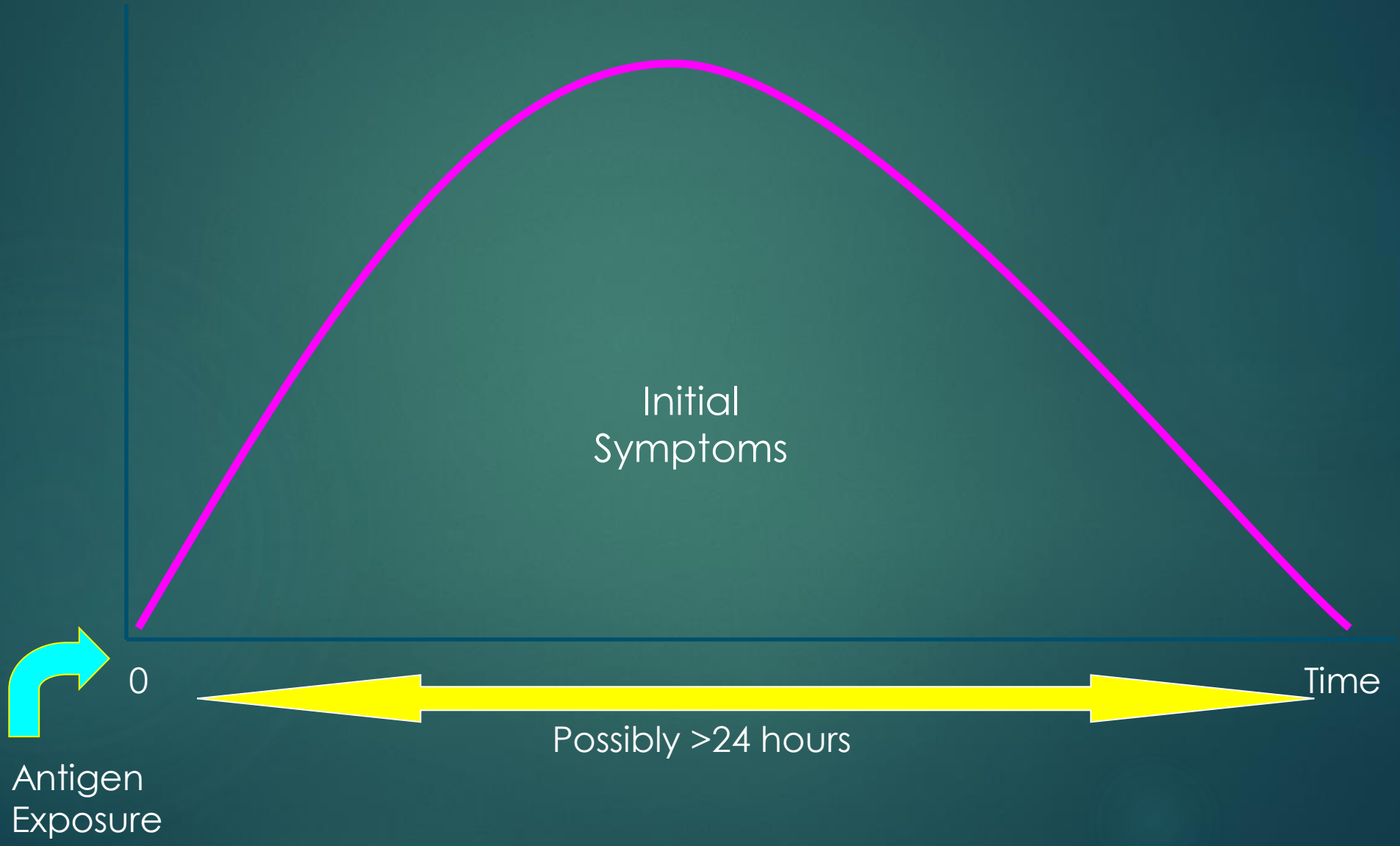


Biphasic anaphylaxis rate

- Adults from 0.4 to 2.2%
- Children 14.7%
- Risks include: delayed use of epinephrine, food allergy, previous biphasic reaction

Curr Opin Allergy Clin Immunol 2016, 16:346–351

Protracted Anaphylaxis



Anaphylaxis: Key Questions

- Suspected trigger
  - Amount/dose
  - Preparation of food (raw, cooked, baked)
- Symptoms and timing – consistent with anaphylaxis?
- Treatment: time given and response to treatment
- Associated factors: exercise, medications, food, infection, alcohol
- Records of acute event (ER visit)
  - Can be very helpful to see vital signs, physical examination in cases where all symptoms subjective

Anaphylaxis: Lab Diagnosis

- Serum Tryptase
  - Mast cell mediator released early in a reaction
  - Measurable between 15 minutes and 3 hours after reaction
  - Often not detected in food-induced reactions (<20-35%)
  - May be elevated in absence of anaphylaxis (e.g., mastocytosis, mast cell activation disorder, post-mortem) so elevated levels do not necessarily indicate anaphylaxis
  - Plasma histamine elevated initially, correlates with severity, but need to measure 5 to 15 minutes after reaction
- Urinary metabolites (N-methylhistamine, PGF2-alpha) longer lasting, can be measured in 24-hour urine sample
- Labs support diagnosis of anaphylaxis if positive, but do not rule out anaphylaxis if negative

Anaphylaxis: In Search of the Culprit!

- Direct testing (skin testing, serum specific IgE) based on patient history
  - Not in "screening" fashion
- Allergen specific IgE (positive serum sIgE) indicates sensitization
  - Not always clinically significant
  - Must correlate history and testing

Treatment & Management

Anaphylaxis: In Search of the Culprit!

- Refer to Allergist/Immunologist for evaluation/management
- May evaluate for specific IgE (skin and/or blood testing) to allergens such as:
  - Foods
  - Insect venoms
  - Medications
  - Latex
- May consider challenge under medical supervision, depending on history/test results
- **Evaluation directed and based on history**

Epinephrine

- The most effective treatment for anaphylaxis
- a and β adrenergic receptor agonist
  - a reverses peripheral vasodilatation, hence increasing BP and coronary artery perfusion
  - β-1 inotropic/chronotropic effects increase heart rate, contraction strength
  - β-2 relaxes smooth muscle around airways (bronchodilator)
- No absolute contraindication for treatment of anaphylaxis
- Failure to administer early in reaction repeatedly linked with fatalities
- Do not rely on antihistamines, bronchodilators

Bock, S.A., et al. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001 Jan; 107: 191–193

Epinephrine

- Many deaths in anaphylaxis are due to obstruction to airflow in the upper and/or lower respiratory tract that result in respiratory failure and vascular collapse
- If you wait for the patient to develop shock, you have waited too long!
- Treat long before signs and symptoms of cardiovascular collapse occur!

Bock et al. J Allerg Clin Immunol 2007;119:1016-1018.

Management: Immediate Treatment

- EPINEPHRINE
  - Primary and most important treatment
  - Dose
    - Adults 0.3-0.5 mg of 1:1000 IM; max of 0.5 mg
    - Children 0.01 mg/kg of 1:1000 IM; max 0.3 mg
- Repeat doses every 5 min or sooner if needed
- Call 911/activate EMS after administration
  - For observation/continued treatment, NOT because epinephrine is dangerous
- Keep patient lying down or in a semi-recumbent position – do not ask to stand up, do not support in sitting position if unconscious
  - Change to a more upright posture or continuing to be supported in sitting position when unconscious during anaphylaxis were reported to result in sudden death[1]
  - May place on side if unconscious or vomiting
- Always give epinephrine first before asthma reliever puffer for airway symptoms in patients with both asthma and food allergy

When to Transition to "Adult" Epinephrine Auto-injector Dose?

- Three dosing options of epinephrine auto-injector (EAI) (0.1, 0.15, & 0.3 mg)
  - Alternative to EAI is having patients/families dose via ampule/syringe
    - Associated with increased potential for dosage errors, particularly during reactions
- Expert consensus in North America: transition otherwise healthy children to 0.3 mg dose at 25 kg
  - **Note**: differs from package insert, but this recommendation made after weighing risks/benefits, particularly of under dosing vs overdosing

Simons FER. J Allergy Clin Immunol 2004;113:837-44
Sicherer SH, Simons FE; Section on Allergy and Immunology, American Academy of Pediatrics. Pediatrics 2007 Mar;119(3):638-46

Outdated Epinephrine Loses Efficacy

- With time, percent of dose and bioavailability reduced
- Improper storage and exposure to sunlight and heat increase degradation
- Degradation often occurs without a color change in the epinephrine solution
- BUT EXPIRED EPINEPHRINE IS BETTER THAN NO EPINEPHRINE!

Simons FER et al. J Allergy Clin Immunol 2000;105:1025-30

Ongoing knowledge gaps in physicians and patients

- Inadequate knowledge of epinephrine use
- Lack of awareness of EAI doses
- Incorrect prescribing
- Incorrect usage of EAI
- Failure to carry EAI
- Out of date EAI
- False belief in "absolute contraindications" to use of epinephrine for anaphylaxis
- Reliance on inhaled bronchodilator therapy for airway symptoms in lieu of epinephrine

Altman AM et al., J Allergy Clin Immunol 2015 Mar;135(3):830-3; Clark S et al., J Allergy Clin Immunol 2014;134:1125-30

Grouhi M et al., J Allergy Clin Immunol 1999; 104:190-3; Huang SW. J Allergy Clin Immunol 1998;102:525-6

Jacobs TS et al., Pediatr Allergy Immunol 2012;23:582; Kastner M et al ., Allergy 2010 65(4): 435-44; Sicherer SH et al. Pediatrics 2000; 105:359-62; Wood RA et al., J Allergy Clin Immunol 2014;133:461-7

Auto-injectable Epinephrine Devices

- Epi-pen®
- Generic Epi-pen®
- Auvi-Q®
- Adrenaclick®
- Generic Adrenaclick
- Teva®

Accidents Are Never Planned

Emergency medications and a treatment plan must be immediately available and accessible at all times!

3 Rs of an Anaphylaxis Emergency Action Plan

1. **R**ecognize symptoms early
2. **R**espond quickly
3. **R**eview what caused the reaction

Anaphylaxis Emergency Action Plan

An Anaphylaxis Emergency Action Plan should include:

- Relevant allergens
- What symptoms to look for
- Use EAI
- What dose of medication
  - Increase epinephrine to 0.3mg dose at/above 25kg weight
- Where EAI are kept
- What others should do
  - PRIORITIZE calling EMS or 911
  - Keep patient supine or in position of comfort
- Anaphylaxis emergency practice drills

Example: Anaphylaxis Emergency Plan

- https://www.aaaai.org/aaaai/media/medialibrary/pdf%20documents/libraries/anaphylaxis-emergency-action-plan.pdf

American Academy of Allergy Asthma & Immunology
www.aaaai.org

Anaphylaxis Emergency Action Plan

Patient Name: _____ Age: _____

Allergies: _____

Asthma ☐ Yes *(high risk for severe reaction)* ☐ No

Additional health problems besides anaphylaxis: _____

_____

Concurrent medications: _____

_____

Symptoms of Anaphylaxis

MOUTH	itching, swelling of lips and/or tongue
THROAT*	itching, tightness/closure, hoarseness
SKIN	itching, hives, redness, swelling
GUT	vomiting, diarrhea, cramps
LUNG*	shortness of breath, cough, wheeze
HEART*	weak pulse, dizziness, passing out

Only a few symptoms may be present. Severity of symptoms can change quickly.
**Some symptoms can be life-threatening. ACT FAST!*

Emergency Action Steps - DO NOT HESITATE TO GIVE EPINEPHRINE!

1. Inject epinephrine in thigh using (check one):
   - ☐ Adrenaclick (0.15 mg) ☐ Adrenaclick (0.3 mg)
   - ☐ Auvi-Q (0.15 mg) ☐ Auvi-Q (0.3 mg)
   - ☐ EpiPen Jr (0.15 mg) ☐ EpiPen (0.3 mg)
   - Epinephrine Injection, USP Auto-injector- authorized generic
     - ☐ (0.15 mg) ☐ (0.3 mg)
     - ☐ Other (0.15 mg) ☐ Other (0.3 mg)

Specify others: _____

IMPORTANT: ASTHMA INHALERS AND/OR ANTIHISTAMINES CAN'T BE DEPENDED ON IN ANAPHYLAXIS.

2. Call 911 or rescue squad (before calling contact)

3. Emergency contact #1: home_____ work_____ cell_____

   Emergency contact #2: home_____ work_____ cell_____

   Emergency contact #3: home_____ work_____ cell_____

Comments: _____

_____

_____
Doctor's Signature/Date/Phone Number

_____
Parent's Signature (for individuals under age 18 yrs)/Date

For Patients and Providers

- Wallet card
- Emergency action plan
- Educational materials
  - www.aaaai.org
  - www.foodallergy.org

Did you know about all the options?!

Epinephrine Autoinjector

Overall, 79% of ED patients with anaphylaxis had an EAI prescribed and 22% had an allergist referral; 71% picked up the EAI from the outpatient pharmacy, EAI dispensing changes occurred, and training was infrequent. Collaboration between emergency medicine clinicians, allergists, and pharmacists is needed to streamline treatment and follow-up.

(Allergy Asthma Proc 44:283-290, 2023; doi: 10.2500/aap.2023.44.230023)

Cash Pay Prices of Epinephrine Autoinjectors

- Walgreens:
  - Mylan $341.29
  - Teva $341.29
  - Good Rx $287.29
- Genscripts:
  - Mylan $310.58 (does not carry in house)
- Costco
  - Mylan $704.71 (having issues with obtaining d/t Pfizer
  - Costco membership $686.79
  - Good Rx $330.66
- Walmart:
  - Teva $277.78
  - Good Rx $179.95
- Sam's Club:
  - Teva $490
- CVS:
  - Adrenaclick $110.00
  - GoodRx $154.58


Emergency
Kit


American Academy of
Allergy Asthma & Immunology

QUESTIONS?

jpurser@allergyclinicoftulsa.com