

# Anaphylaxis:

What is it?

How should anaphylaxis be treated?

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# Anaphylaxis: What is it?

# Definition: Anaphylaxis

1. Effects Entire Body, immediate, allergic reaction caused by IgE mediated release of Mast Cell (and Peripheral Blood Basophil) mediators.
  1. Requires two or more body systems undergo an allergic reaction
    1. Skin plus respiratory, gastrointestinal, cardiovascular
  2. Presence of shock alone

# Most Frequent Signs and Symptoms of Anaphylaxis

Manifestation	Percent
Hives/Swelling	88
Upper airway swelling	56
Shortness of Breath/wheeze	47
Flush	46
Low Blood Pressure	33
Gastrointestinal	30

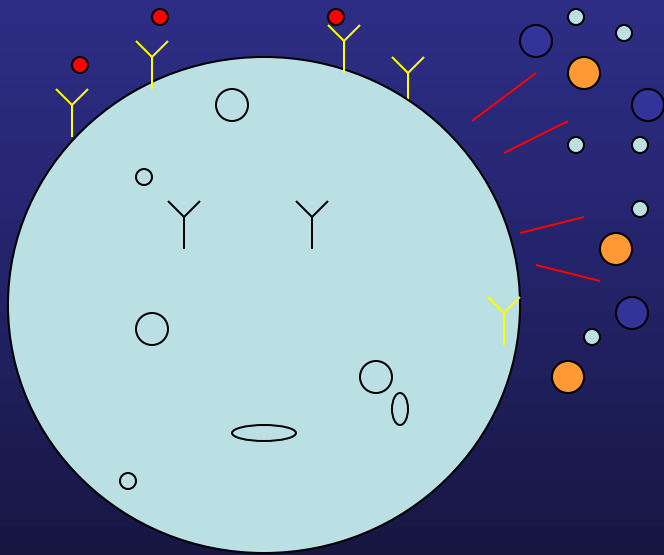
# Symptoms

- Skin >90%
  - Hives or Swelling 85-90%
  - Flush 45-55%
  - Itching without rash 2-5%
- Respiratory 40-60%
  - Wheeze 45-60%
  - Swelling of the throat 45-50%
  - Runny nose 15-20%
- Vascular Release (Dizziness, Fainting, Low Blood Pressure)

- Abdominal Symptoms (Nausea, vomiting, diarrhea, cramping) 25-30%
- Miscellaneous: Headache, Substernal Pain, Seizure
- Symptom Onset: Immediate to two hours.

# Anaphylaxis Physiology: Histamine and a WHOLE LOT MORE!

IgE  
Antibody



Mast Cell

Histamine  
Leukotrienes  
Prostaglandins  
Thromboxane  
PA Factor



Vasodilation

Smooth Muscle Spasm

Mucus Secretion

Vascular permeability

Eosinophil Activation

DIC

# IgE Mediated Mast Cell Release

- Histamine:
  - H1 Receptor:
    - Vascular Bed Dilates and becomes leaky (Via increased NO excretion)
    - Coronary Artery Spasm
    - Lung and Stomach smooth muscle contraction
    - Increases mucus stickiness
  - H2 Receptor:
    - Direct Vascular Bed Dilation.
    - Increases heart oxygen demand
    - Increases mucus secretion.

- Products of Arachidonic Acid Metabolism (leukotrienes, thromboxane, prostaglandins, platelet-activating factor)
  - Smooth muscle spasm: Wheezing, Diarrhea, Vomiting, Heart Attack.
  - Mucus Secretion:
  - Blood Vessel Dilation: Hypotension
  - Blood Vessel More Leaky: Low Blood Pressure, Swelling , Hives.
  - Eosinophil Activation: Inflammation, Late-phase response
  - DIC

- Chemoattractants: Recruit inflammatory cells.
- Proteoglycans: Increase severity of reaction
- Neutral Proteases: Increase severity of reaction
- Recruitment of the kinin, clotting, and complement systems.

# Cardiovascular Dynamics During Shock

Mast Cell Mediators



Blood Vessel Dilates and is More  
Leaky



Decreased Blood Volume in The Vessels



Low Blood Pressure



Increased Heart Rate



Increased Cardiac Output Initially  
then Decreased Cardiac Output

# 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

# Uniphasic Anaphylaxis

Treatment



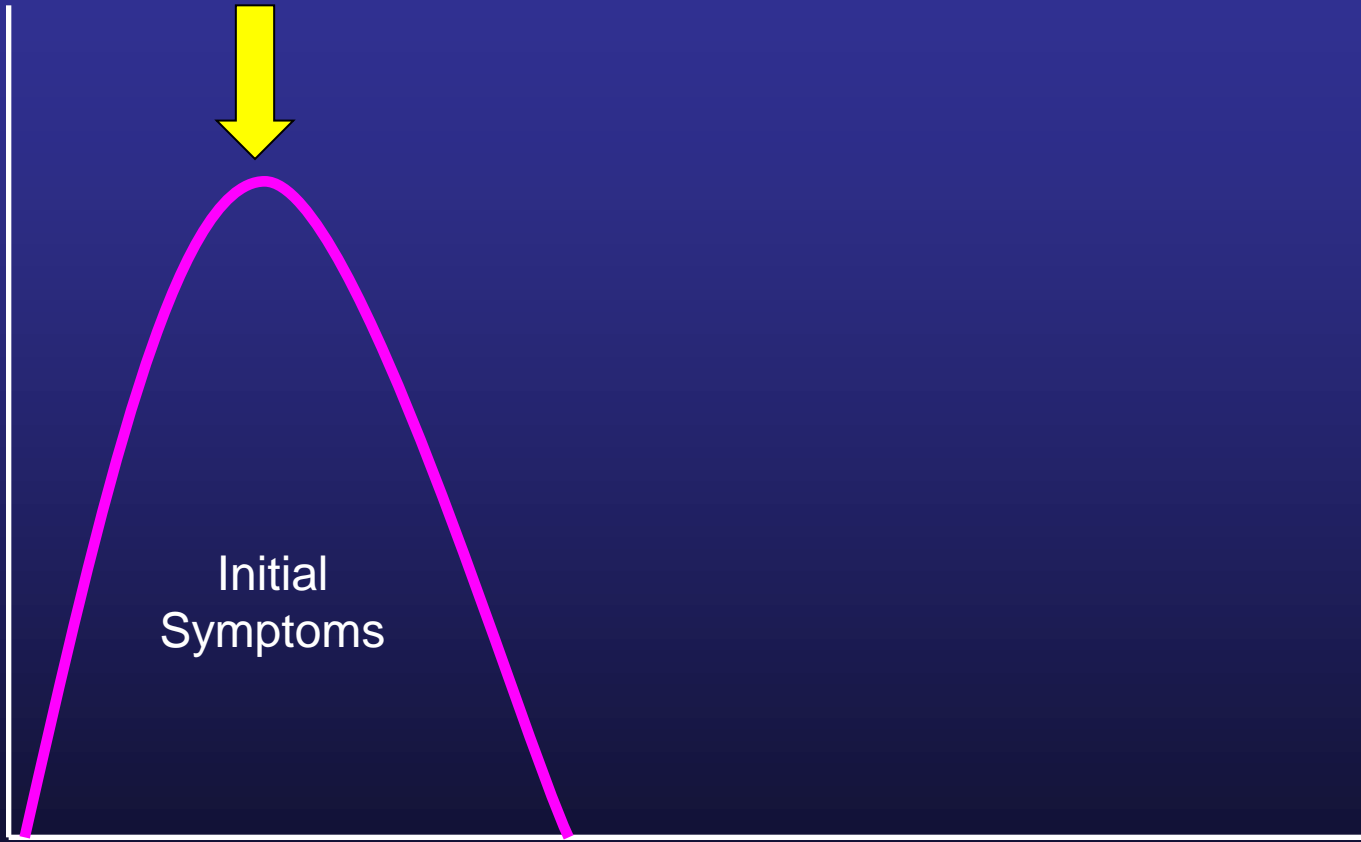
Initial  
Symptoms



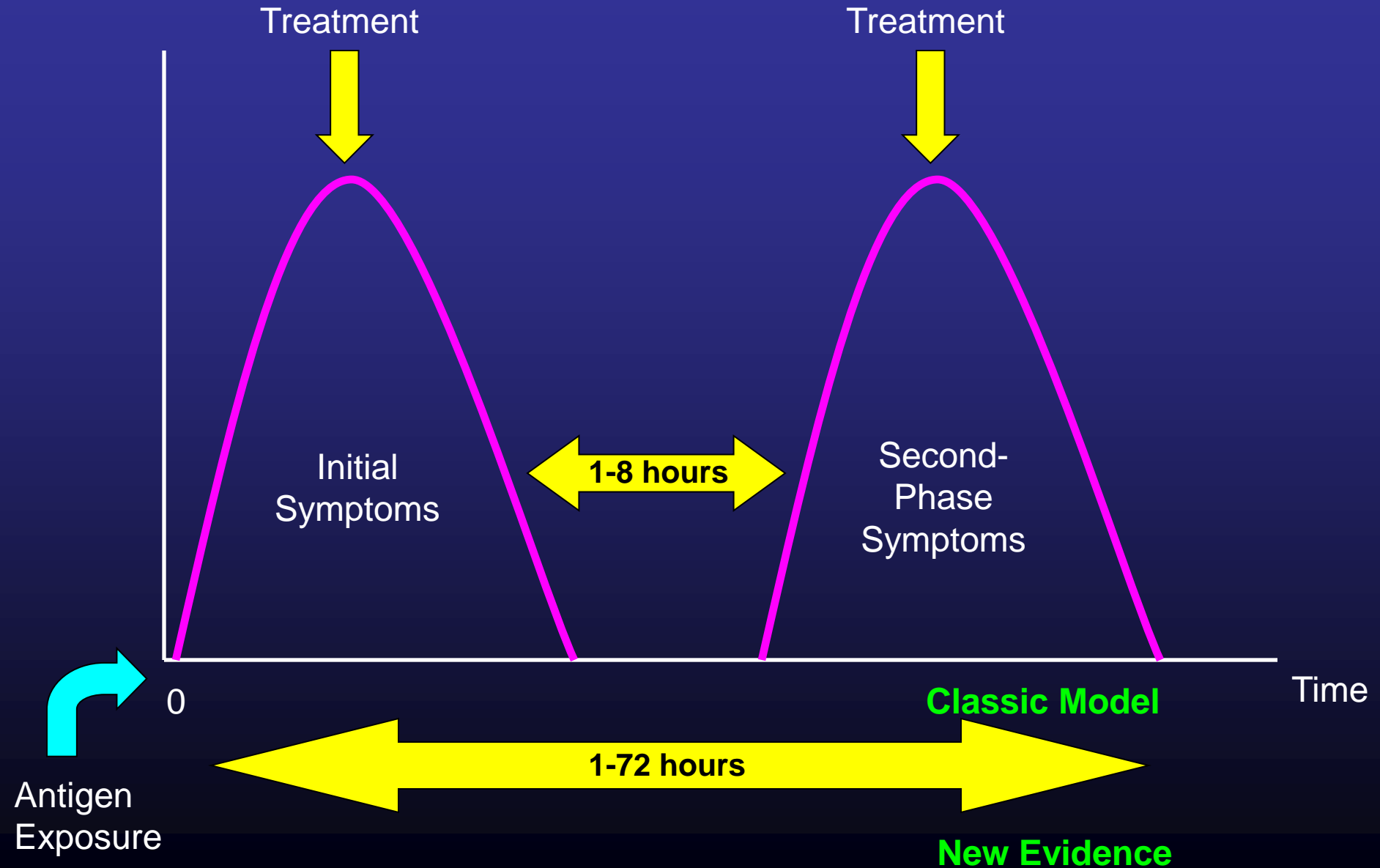
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Time

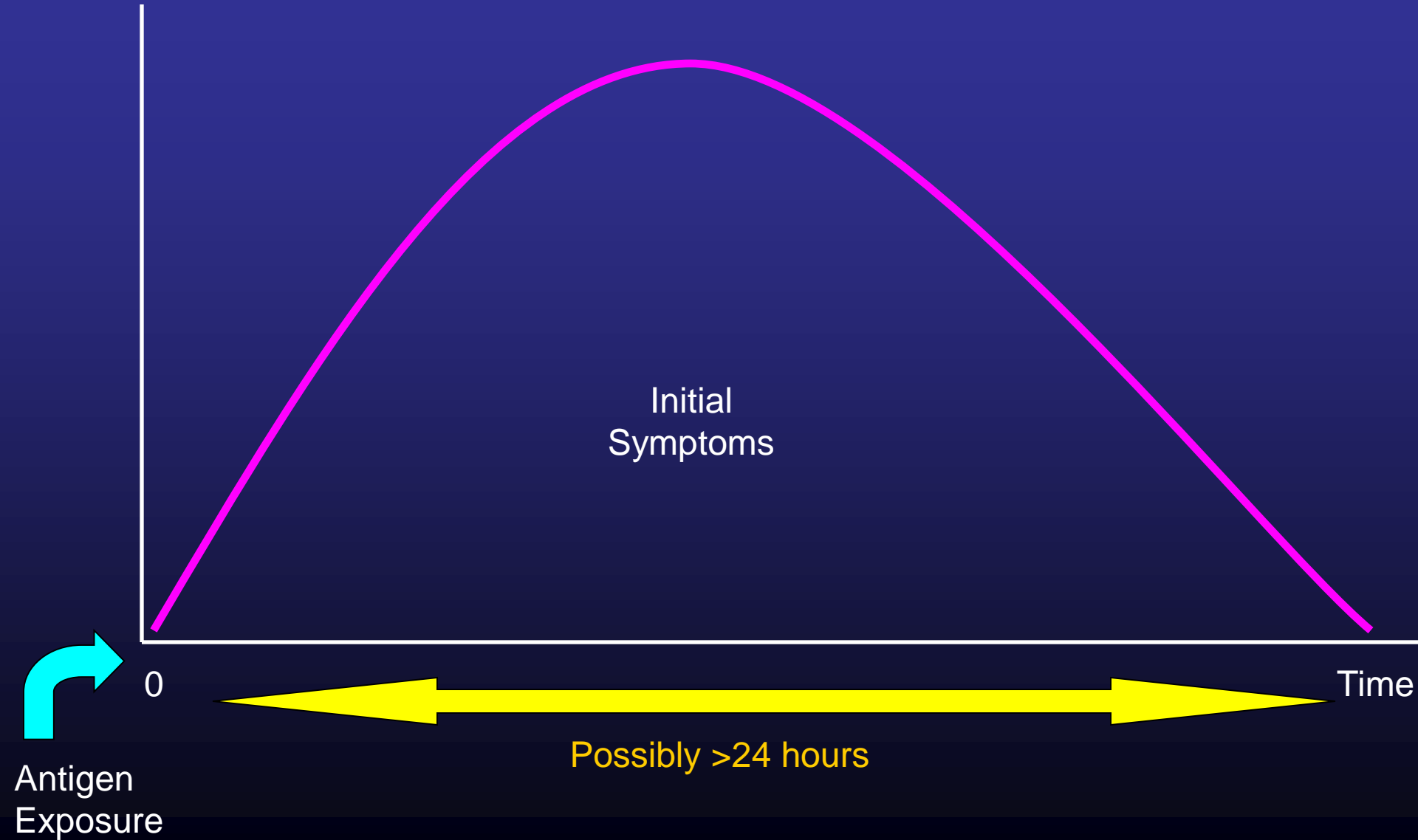
Antigen Exposure



# Biphasic Anaphylaxis



# Protracted Anaphylaxis



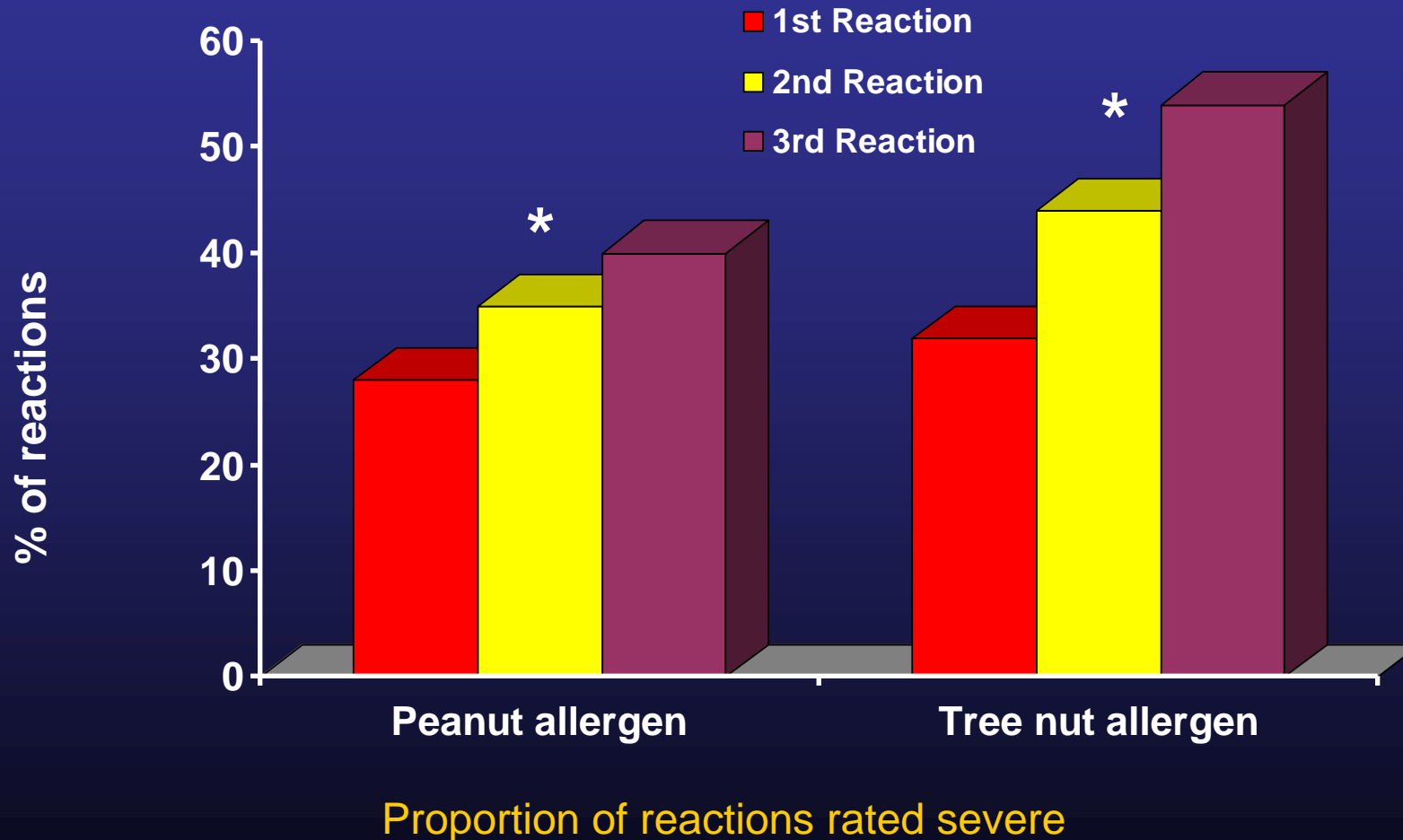
# Factors Affecting Incidence of Biphasic Anaphylaxis

- A delay of 30 minutes or more after exposure before onset of symptoms (Sullivan)
- Initial Low Blood Pressure (Brady)
- Ingested Allergen (Food/Drug)
- Severity of initial reaction
- Delay in administration of epinephrine (Lee)
- Failure to give epinephrine or diminished dose (Brazil)

# Anaphylaxis Death

- Usually occurs within one hour of onset of anaphylaxis.
- 1/3 of Cases occur during a biphasic reaction
- The majority of cases on autopsy showed upper airway swelling in 60% of patients and bronchial obstruction with hyperinflation in 50% of cases.
- Risk Factors:
  - Asthma
  - Type of Exposure: Injection (venom/drugs) > Oral
  - Delay in the use of Epinephrine
    - 62% of patients who died of anaphylaxis had Epinephrine available but only 20% used it prior to cardiovascular collapse.

# Subsequent Reactions May Increase in Severity with Time



# How Should Anaphylaxis Be Treated?

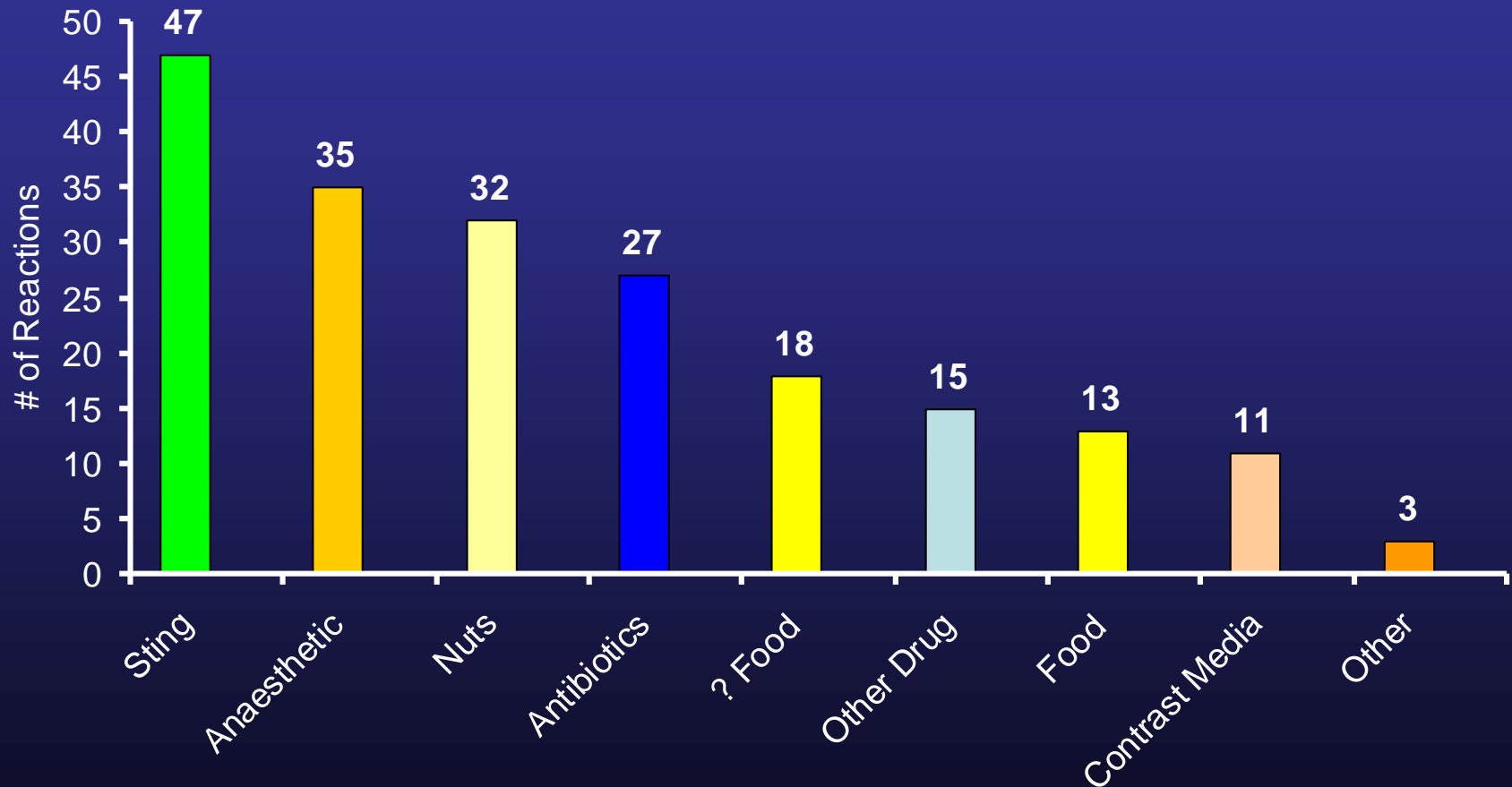
# Define Risk

- History
- Testing
  - Skin Testing
  - IgE CAP RAST Testing

# History

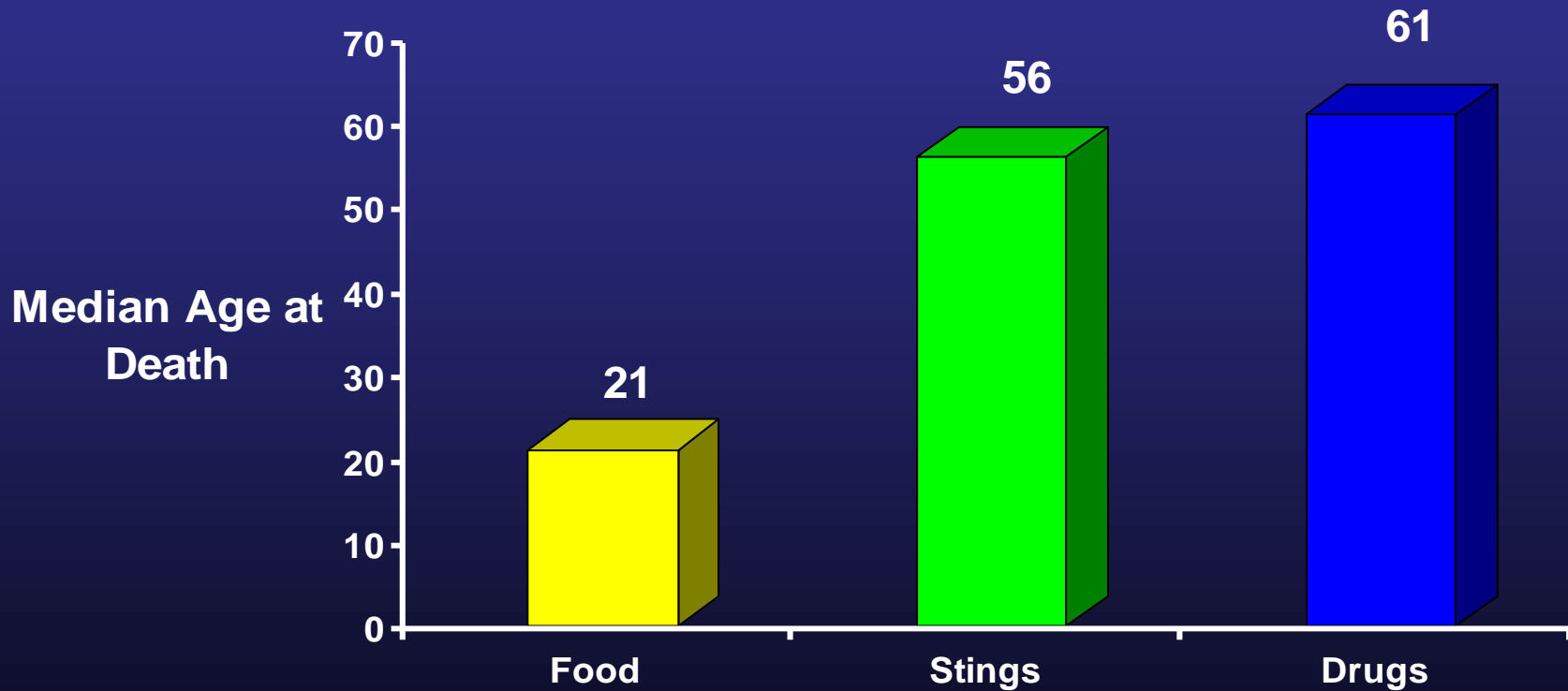
- Increased Risk of Anaphylaxis:
  - Previous Life Threatening Anaphylactic Reaction
  - Asthma
  - Allergen injected > Allergen Oral

# Etiology of Fatal Reactions



# Fatal Anaphylactic Reactions

## Triggers Vary with Patient Age



# Define Risk: Testing

- Skin tests and Blood Tests should be used in combination to determine risk of life threatening reaction.
  - Increased Wheal Size is Associated with Increased Risk.
  - Increased IgE Rast Level is Associated with Increased Risk.
- If Testing is Negative, an Oral Challenge should be performed.
- Testing in the absence of an appropriate history is not helpful

# IgE Rast Level is Predictive of Clinical Severity

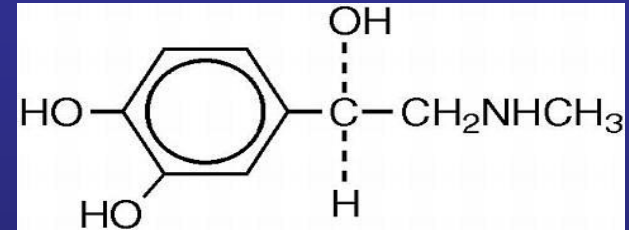
- Egg
  - <2 y.o.: 7kU/L
  - >2 y.o.: 2 kU/L
- Milk
  - <1 y.o: 15kU/L
  - >1 y.o: 5kU/L
- Peanut: 14 kU/L
- Fish: 20 kU/L
- Soy: 30 kU/L
- Wheat: 26 kU/L
- Tree Nuts: 15 kU/L

# Appropriate Treatment

- Epinephrine: Mainstay of therapy

- Action of Epinephrine

- Dilates Airways
    - Constricts Blood Vessels
    - Increases Mucus Clearance
    - Makes Blood Vessels Less Leaky
    - Inhibits Mast Cell Release
    - Inhibits Eosinophil function
    - Primes the Steroid Receptor



- \*\*\*\*Studies show that the earlier it is given the less likely one is to die\*\*\*\*

- Adult dosing 0.3 – 0.5 ml of 1:1000
- Children 0.01 mg/kg. Essentially 60 pounds or more give 0.3 ml of 1:1000. Less than 60 pounds given 1.5 ml of 1:1000
- Repeat every 10-15 minutes.
- Data suggest that up to 35% of patients require more than a single epinephrine injection

# Anaphylaxis Therapy Cont.

- Antihistamines:
  - Combination H1 and H2 better than H1 alone
  - Benadryl (Diphenhydramine) 12.5-50 mg PO or IM
- Lying Down (Trendelenberg Position)
  - Associated with decreased death.
- Inhaled Beta-Agonists (Albuterol)
- Call 911

# Treatment

- Problems found in studies regarding management of anaphylaxis.
  - ER docs fail to prescribe injectible epinephrine
  - Patients are not correctly instructed
  - Patients don't carry the injector with them
  - Patients don't administer epinephrine in a timely fashion
  - A Second dose of Epinephrine is not given when necessary
  - Subcutaneous not intramuscular injections are given.
  - Epinephrine not given in the lateral aspect of the thigh.

# Outdated Epinephrine Loses Efficacy

- As age increases, percent of labeled dose and bioavailability is reduced
- Improper storage and exposure to sunlight and heat increase degradation
- Color change may signal deterioration
  - Lack of color does not verify efficacy

# Inadequate Knowledge of Epinephrine Usage

- Healthcare professionals and patients have inadequate knowledge about outpatient use
  - 76% of physicians are unaware that two EpiPen dose formulations exist
  - Only 55% of patients at risk have in-date auto-injectors on hand
  - Only 30%-40% know how to use auto-injectors correctly

# Epinephrine Is Underutilized for Acute Treatment

- Only about 30% of individuals requiring epinephrine during a reaction actually received it (Gold and Sainsbury, 2000)
- In fatal food-induced reactions, failure to use, delayed use, or inappropriate dose are contributing factors to death (Sampson et al, 1992)
- Used in treatment of 62% of fatal reactions but given before cardiac arrest in only 14% of reactions (Pumphrey, 2000)

# Case 1

- 4 year old boy with nasal allergies, eczema and asthma. Accidental exposure to peanut butter sandwich. He took one bite and spit it out. He then developed immediate vomiting. No hives. No Shortness of Breath. What do you do?
- Give Epinephrine and Go to ER.

## Case 2

- 2 year old at preschool. He developed hives after exposure to peanut at age 1. No shortness of breath. No swelling. A playmate had peanut butter and it touched his face. There are hives at the site. No breathing problems. No vomiting. No drooling. What do you do?
- Give Benadryl and Observe

# Case 3

- 4 year old patient with a 2 month history of daily hives at age 1. Testing at that time was positive to milk. He has strictly avoided milk since that time. Patient accidentally consumed ice cream at a birthday party. It has been five minutes and no immediate reaction is obvious. What do you do?
- Nothing. Schedule testing with an allergist immunologist confirm or reject food allergy.

# Case 4

- An 8 year old girl developed **immediate hives** around the mouth at age 2 after eating **egg**. She was given Benadryl and symptoms resolved. There **may have been shortness of breath** at the time. She was given epinephrine from her PCP and told to avoid all egg. She has not had any egg since that time. She is at a Chinese restaurant and is eating a fish dish (No shellfish). She begins to develop **blotching of the face**. Of note she does have known **eczema** of the face. What do you do?

- An 8 year old girl developed **immediate hives** around the mouth at age 2 after eating **egg**. She was given Benadryl and symptoms resolved. There **may have been shortness of breath** at the time. She had testing done and she had a **4+ skin reaction to egg and RAST blood test was > 20 kU/L**. She was given epinephrine and told to strictly avoid egg. She has not had any egg since that time. She is at a Chinese restaurant and is eating a fish dish (No shellfish). She begins to develop **blotching of the face**. Of note she does have known **eczema** of the face. What do you do?

- An 8 year old girl that developed **immediate hives** around the mouth at age 2 after eating **egg**. She was given Benadryl and symptoms resolved. There **may have been shortness of breath** at the time. She had testing done and she had a **4+ reaction to egg** and RAST was **> 20 kU/L**. She was given epinephrine and told to return for repeat testing in 1-2 years. She returned at age 5. Skin testing at that time was **1+** and RAST was **< 1 kU/L**. She was told to return for oral challenge, but she did not return. She has not had any egg since that time. She is at a Chinese restaurant and is eating a fish dish (No shellfish). She begins to develop **blotching of the face**. Of note she does have known **eczema** of the face. What do you do?

# The Bottom Line

# How should anaphylaxis be treated?

- Use the best medical information to define the risk of an anaphylactic reaction
- Plan before hand what you will do based on the risk.
- If there is a reaction, follow the plan.
- If there is a question, GIVE Injectable Epinephrine and call 911.

A New Treatment Option:  
Twinject™ Auto Injector  
(epinephrine injection, USP 1:1000)

# Twinject™ Product Overview



There are no absolute contraindications to the use of epinephrine in a life-threatening allergic reaction

# Product Overview

- First product introduced to epinephrine auto-injector market since 1982
- First and only FDA-approved epinephrine auto-injector with two doses for the treatment of anaphylaxis
- Manufactured by Hollister-Stier and distributed by Verus Pharmaceuticals

# Dual-Dose Availability

- Twinject™ offers availability of a second epinephrine dose in a single unit
  - Up to 35% of patients may require more than one dose to effectively treat anaphylaxis
  - First injection administered using auto-injector
  - Second dose, if needed, is in a pre-filled syringe inside the barrel of the Twinject™ injector
- Pre-filled, pen-sized auto-injector with two 0.3 or 0.15 mg epinephrine doses
  - Also available in 2-Pack packaging

Twinject is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical care

# Twinject™ Product Features

	Twinject™
Available Doses	0.3 mg (single and 2 Pack) & 0.15 mg (single and 2 Pack)
Doses Per Injector	2 inseparable doses in one injector
Second Dose Administration	Available Manual injector included inside the barrel of Twinject™

Twinject should be used with extreme caution in people who have heart disease. Side effects of Twinject may include fast or irregular heartbeat, nausea, and breathing difficulty. Certain side effects may be increased if Twinject I used while taking tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs)

# Twinject™ Product Features

	Twinject™
Packaging	Permanently attached wrap label patient instructions Crush-resistant container with clip
Needle Size	Thin 25 gauge ½ inch exposed needle length
Noise Level	Quiet operation reduces risk of removal from injection site
Cost / Formulary Position	AWP Single \$68.04 AWP Two-Pack \$114.60 Expected 2 <sup>nd</sup> or 3 <sup>rd</sup> Tier

Please refer to the Twinject package insert for complete prescribing information, including important warnings, precautions, safety, dosing and storage information.

# Twinject™ Product Photos



# Twinject™ Patient Support & Educational Tools

- Twinject™ Demonstrators
- Patient instructional DVDs
- Patient education brochures
- Nurse educational materials
- FAAN's "Getting Started" Brochure
- \$15 Co-Pay Coupons
- [www.twinject.com](http://www.twinject.com)

# Conclusions

- Twinject™ offers patients ready access to a second dose of epinephrine
  - Up to 35% of anaphylactic reactions may require more than a single dose to treat
  - Critical in a biphasic or protracted reaction – which is unpredictable
- Additional Twinject™ product features:
  - Crush resistant carrying case
  - Permanently attached wrap label instructions
  - 25 gauge needle
  - Quiet firing mechanism