Facing Food Allergies

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Learning Objectives

- Prevalence
- Spectrum of food allergies
- Diagnosis
- Family Education
- Drugs of choice
- Prevention
  - Peanut
  - Other foods
- Future treatments of allergy

Prevalence

- Affects 4 - 6% of children in the US.
  - Reported 15 million people have food allergies.
  - 1 in 13 children have food allergy.
- 50% increase in food allergies among children from 1997-2007 per 2013 CDC report.
- 2006 CDC report found 88% of schools have ≥ 1 child with food allergy.

Local Impact: CHOP

- 41,000 patients identified as having food allergy in electronic record.
  - 29.6% are allergic to more than one food.
- 61.2% seen in the Allergy department are allergic to more than one food.

Importance

- 3.5 fold increase in hospitalizations between 2000-2006 due to food allergy (CDC).
  - 9,500 hospital discharges per year with diagnosis related to food allergy.
- Economic cost is $25 billion per year in US.
Peanut allergy

- Peanut allergy prevalence has **tripled** in past 15 years.
  - Affects > 1% of the population
- 100,000 new cases per year in the US and UK.
- 1:50 primary school children in US, UK, CA, Australia.
- Incidence is increasing in developing countries like Ghana.

**Natural History**

- About 85% of cows milk, soy, egg and wheat resolve by 3 years of age.
  - One study found that children are taking longer to outgrow milk and egg allergy.
  - May be more like 6-8 years old.
- Peanut, tree nut, seafoods and seeds typically persist.

**Spectrum of Food Allergies**

- IgE Mediated
  - Focus of today’s talk
- Non IgE mediated
  - Food protein induced enterocolitis syndrome
- Mixed
  - Eosinophilic Esophagitis

**Food Protein Induced Enterocolitis Syndrome: FPIES**

- Non-IgE mediated food allergy.
- Typically presents in infancy.
- Prevalence varies by studies, may be under-reported.
- Characterized by repetitive, protracted vomiting that begins approximately 1-4 hours after eating the food. Usually 2.5 hours after the food is ingested.
  - The vomiting is often accompanied by decreased activity or lethargy and pallor, and potentially later followed by diarrhea.
  - Different from anaphylaxis because: Delayed onset and absence of cutaneous and respiratory symptoms.
- Children are sick. Treatment is IV fluids during acute episodes.
  - Symptoms usually resolve within 24 hours.
  - Some are chronic.

**FPIES**

- Typically with 18-24 months of avoidance, symptoms resolve.
- Guidance is strict avoidance.
- Give families letter to carry in case an ED visit is required— that fluids are treatment. (Saves against unnecessary work-up and tests).
- Offending foods:

<table>
<thead>
<tr>
<th>Mkt.</th>
<th>most common</th>
<th>Rice</th>
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<tbody>
<tr>
<td>MF (most common)</td>
<td>Soy</td>
<td>Meat &amp; Poultry</td>
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<tr>
<td>Other grains: oat, barley, corn</td>
<td>Egg</td>
<td></td>
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<tr>
<td>Vegetables: white potato, sweet potato</td>
<td>Fresh banana, apple</td>
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**Resource for providers:**

- International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome.
  - Currently in press in the Journal of Allergy and Clinical Immunology.
- The International FPIES Association - [http://www.fpies.org](http://www.fpies.org)
  - Family resource too!
**Eosinophilic Esophagitis: EoE**

- Characterized by severe, often isolated, GERD-like symptoms, including chest pain, emesis, heartburn, feeding difficulties, dysphagia.
  - Seen in oral immunotherapy to foods
  - Reflux can cause these symptoms too! Start PPI then scope to know.
- Seen in 1/2000 of general population
  - More common in boys (3:1 ratio)
- Development of eosinophils in the esophagus. Patients treated with reflux medications for management. Diagnosis made by biopsy based on number of eosinophils per high power field.
- Symptoms vary with age
  - Reflux symptoms (infants and toddlers)
    - Vomiting, regurgitation, growth concerns
    - Heartburn, epigastric pain
  - Abdominal pain in school-age children
  - Dysphagia (more in adolescents and adults)
    - Food impactions
- **Treatment**: elimination diets, swallowed steroids, oral steroids
- Co-manage GI and Allergy

**Resources for providers:**
- Evidence based approach to diagnosis and management of Esophageal Eosinophilia and EoE- American Journal of Gastroenterology
- American Partnership for Eosinophilic Disorders- https://apfed.org

**CASE # 1:**

Amelia is a 5 month old with diffuse eczema who is breastfed and starting solids. Family is reluctant to use topical steroids and management is difficult. They feel strongly she is allergic to a food.

They want “a full work up for food allergies.”

What do you do?

**Making the Diagnosis**

- No IgE panel of foods!
- Try to treat skin first, educate about eczema management
- If the family feels the child had overt symptoms after ingestion of a food, can order an IgE to that specific food. But best probably to wait!
• History!
  - Reaction is less than 30 minutes (up to within 2 hours) after exposure of a food, symptoms were noted.

• Gold standard to diagnose: oral food challenge to the food of concern.
  - Give small increasing amounts of the food in supervised setting until a serving size is reached.

• Skin testing
  - ≤ 50% positive predictive value
  - ≥ 95% good negative predictive value

• Specific IgE testing
  - 85% sensitive, 40-80% specific

Preparing families for an allergic reaction

• Administer epinephrine unless mild reaction

• Epinephrine Auto-injector doses:
  - Epinephrine JR (0.15 mg) IM for children < 25 kg
  - Epinephrine (0.3 mg) IM for children ≥ 25 kg

• Two strengths for each—0.15 mg/injection and 0.30 mg/injection

• Auto-injector options now:
  - EpiPen
  - Auvi-Q
  - Generic auto-injector
  - CVS generic auto-injector
  - Many copay assistance and coupons for each device.

Epinephrine

Side Effects:
• Jittery, tachycardia, hypertension, headache, dizziness
• Rare: arrhythmias, nausea, vomiting
• Greater risk of SE with IV administration

*The only medicine that will stop an allergic reaction.

Benefits of giving Epinephrine outweigh the risks!

Antihistamines: H₁ Blockers

H₁ Blockers
First generation: Diphenhydramine (Benadryl)
  - Dose: 1 mg/kg q 6 hrs
  - Max: 50 mg
  - Sedating

Second generation: Cetirizine (Zyrtec)
  - Less sedating
  - Longer duration of action
  - Similar onset and efficacy as Diphenhydramine

Liquid is faster than pills (30 minutes)
Antihistamines: H₂ Blockers

H₂ Blockers
- No evidence for children
- Faster resolution: cutaneous symptoms, tachycardia
- May be helpful for GI-related symptoms
- Medication of choice in category- Ranitidine (Zantac)

Bronchodilators

Albuterol
- Adjunctive therapy only
- Does NOT take the place of epinephrine
- Nebulized 0.01-0.05 mL/kg of 0.5% solution every 15 minutes as needed

Corticosteroids

- Onset within 4-6 hours
- Potentially prevent protracted or biphasic anaphylaxis
  - Lack of studies
- Benefit for children with asthma
- Effective in dye prophylaxis

Dose:
  - Methylprednisolone-1-2 mg/kg/day
  - Prednisone 0.5-1 mg/kg/day

Additional Treatments

Based on availability at your site:
- Rapid fluid resuscitation
  - 1-2 L of NS for adults, 5-10 mL/kg in first 5 minutes
  - Children should receive 30 mL/kg in first hour
- Pressor support
  - Such as Dopamine
- Glucagon
  - Possible option for refractory hypotension
- Endotracheal intubation

Education for families

- Referral to an allergist
- Skin testing
- Teach avoidance
- Avoid cross-reacting drugs
- Observation period after allergy immunotherapy injections
- Avoidance of β–blockers and ACE inhibitors
- MedicAlert bracelet
- Epinephrine self-injector
- Provide anaphylaxis/emergency plan

Avoidance

- Read labels
  - Top 8 allergens will be listed separately as well
- You have to ingest the food to trigger an allergic reaction. Help reduce anxiety for all family members surrounding the food allergy
  - Much work on health related quality of life impact of food allergy. Constant “on guard,” social isolation...
- Oils are usually safe- i.e. hot pressed peanut oil is safe for peanut allergic patients.
  - Concern is cold pressed oils often found in many Asian cuisines
### CHOP Allergy Anaphylaxis Plan: SYMPTOMS

- **Skin:** “hives” (red blotches or welts that itch), mild swelling, severe swelling
- **Eyes:** tearing, redness, itch
- **Nose:** clear discharge, itch, congestion
- **Mouth:** itch, lip swelling, tongue swelling
- **Throat:** tightness, trouble speaking, trouble breathing in
- **Lungs:** shortness of breath, rapid breathing, cough, wheeze
- **Gut:** repeated vomiting, nausea, abdominal pain, diarrhea (usually later)
- **Heart/Circulation:** weak pulse, loss of consciousness
- **Brain:** anxiety, agitation, or loss of consciousness

### CHOP Allergy Anaphylaxis Plan: TREATMENT

1. **If the child develops only hives or mild skin swelling,** give an antihistamine. Benadryl (diphenhydramine) is preferred
   - Dose: Benadryl __________ teaspoon(s) by mouth. (12.5mg/teaspoon; approximately one teaspoon per 25 lbs of body weight)
   - Observe closely for additional symptoms for the next six hours; notify responsible person.

2. **If the child develops any of the signs of severe reaction or anaphylaxis,** immediately:
   - Give EpiPen/EpiPen Jr/Twinject/AuviQ/AuviQ Jr. (0.___mg) into the fleshy portion of the outer thigh (directions on reverse side).
   - Give Benadryl as above if child can swallow.
   - Arrange for transport to Emergency Room or physician’s office.
   - Albuterol if still wheezing

### Resources

- FARE (Food Allergy Resource and Education) was Food Allergy and Anaphylaxis Network (FAAN)
- Kids with Food Allergies
- American Academy of Allergy, Asthma and Immunology
- American College of Allergy, Asthma and Immunology

### Current Law

- **On November 13, 2013,** President Obama signed into law the School Access to Emergency Epinephrine Act, which encourages states to adopt laws requiring schools to have on hand “stock” epinephrine auto-injectors.

- **In Late 2013,** the CDC created voluntary guidelines ([https://www.cdc.gov/healthyyouth/foodallergies/pdf/13_243135_A_Food_Allergy_Web_508.pdf](https://www.cdc.gov/healthyyouth/foodallergies/pdf/13_243135_A_Food_Allergy_Web_508.pdf)) for managing food allergies in schools and daycare.

### Clinical Pearls

- **At every encounter,** remind them to carry their epinephrine auto-injector.
- It’s possible to outgrow allergens!
- Don’t order panels of IgE testing- costly and many false positives. Even if families keep asking!
Potential explanation for rise in prevalence...

Changes in timing of exposure to allergenic foods:

- Progressive delay in timing of first exposure to solid foods

1960s: Average age 2 months

1970s: Guidelines recommended delay until after 4 months

1990s: Guidelines recommended delay until after 6 months

2000s: Guidelines recommended delay allergenic foods until after 1 year of age.
  Up to 3 years for peanuts.
  (Adapted from K. Allen, 2016)

2008: Development of the first clinical guidelines for the diagnosis and management of food allergy published by NIAID
  – Concluded that insufficient evidence existed to recommend routine food allergy testing prior to the introduction of highly allergenic foods in high-risk children.

- Astute clinicians in the UK observed a difference between countries. In Jewish children in the UK, the risk of the development of peanut allergy was 10 times higher compared with similar age group of children in Israel.

- Striking difference in food consumption. Peanut based foods introduced around 7 months of age.

- Lead to brilliant landmark study...

LEAP study

- 640 children between 4-11 months at high risk for development of peanut allergy—either severe eczema, egg allergic or both.
- Separated the group into a consume and avoid group, skin tested.

Prevalence of Peanut allergy after 60 months:

<table>
<thead>
<tr>
<th>Test</th>
<th>Consumption</th>
<th>Avoidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>10.6%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Negative</td>
<td>1.7%</td>
<td>13.7%</td>
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Summary: Early introduction seems better.

LEAP-On Study

- Assessed persistence of desensitization. Everyone avoided peanut x 12 months. Would LEAP group re-sensitize?

- 556 kids participated then food challenged after 12 months.
  – Consumption group- 4.8% peanut allergy prevalence
  – Avoidance group- 18.6% peanut allergy

- Labs trended downward in the early consumption group, 3 did develop peanut allergy.

There is something important about that early window and the onset of food allergy. Would it work for non-atopic kids?
### Hotly debated topic
- Many groups feel very strongly: AAP, AAAAI, WAO, Breastfeeding groups.
- Nutritional concerns: giving 250 extra cal/day of protein will impact other foods ingested
  - Affect on growth?
- Oral motor concerns eating those foods at such a young age.
- Impact on celiac disease and autoimmune.

### Initial Consensus Guidelines
- "LEAP provided Level I evidence that peanut introduction is safe in highly allergenic group."

Initial 2015 Recommendations:
- Consider peanut introduction if high risk between 4-11 months.
- If early atopic disease like severe eczema, egg allergy, consider allergy evaluation. Possibly skin test.

### Current: NIAID Guidelines 2017
3 levels of risk for food allergies:
1) **No risk**: introduce peanut when age appropriate and accordance with family or cultural practices.

2) **Low risk**: mild-moderate eczema; sibling with food allergy; family history of food allergy

3) **High risk**: severe eczema; egg allergy or both

### No Risk
**Health Nuts Study**: Large birth cohort study from Australia
- Found 14 % with peanut allergy had no risk factor at 12-18 months.

*Encourage introduction!*

### Recommendation for NO or LOW risk
- No allergy testing or screening is necessary.
- Introduction between **4-10 months of age** with peanuts.
- No need for in-office evaluation.
- No evidence exists for restricting allergenic foods in infants without known risks for food allergy.
- “Infants without eczema or any food allergy should have age-appropriate peanut-containing foods freely introduced in the diet together with other solid foods and in accordance with family preferences and cultural practices.”

### Mild-to- Moderate Eczema
- Introduction of age-appropriate peanut-containing food **around 6 months** of age.
- Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready.
- Dietary peanut should be introduced at home without an in-office evaluation.
High Risk: Severe Eczema defined

- Persistent or frequently recurring eczema with typical morphology and distribution.
- Assessed as severe by a health care provider.
- Requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors, or other anti-inflammatory agents despite appropriate use of emollients.

High Risk: Severe eczema ± Egg allergy

- Should have introduction of age-appropriate peanut-containing food as early as 4 to 6 months of age to reduce the risk of peanut allergy.
- Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready.
- It is strongly encouraged that infants be evaluated with peanut-specific IgE, skin prick test, or both before introduction of peanut.

High Risk: Severe Eczema ± Egg Allergy

- A peanut sIgE level of < 0.35 kUA/L has strong negative predictive value for the diagnosis of peanut allergy. Peanut can be introduced at home.
- A peanut sIgE level of ≥ 0.35 kUA/L or greater lacks adequate positive predictive value for the diagnosis of peanut allergy. An infant with a value of 0.35 kUA/L or greater should be referred to a specialist.

* No food allergen panel testing is recommended.

Ways to introduce peanut

- Bamba (used in LEAP study) – peanut puff
  - 21 pieces = 2 grams protein
  - For infants < 7 months, soften with 4-6 tsp of water or breastmilk. For older infants who can manage dissolvable textures, unmodified Bamba can be used.
- Thinned smooth peanut butter – 2 teaspoons (9-10 grams protein)
  - Measure and add 2-3 tsp of hot water slowly. Stir until dissolved. Let cool. Increase water amount if necessary or add previously tolerated infant cereal.

- Smooth peanut butter puree – 2 tsp (9-10 grams protein)
  - Measure peanut butter. Add 2-3 tablespoons of pureed or tolerated fruit or vegetables. You can increase or reduce volume of puree to achieve desired consistency.
- Peanut flour or peanut butter powder – 2 teaspoons (4 grams protein)
  - Measure 2 teaspoons of either. Add 2 Tbsp of pureed tolerated fruit or vegetable to flour or powder.
Handouts available online from NIAID summarizing guidelines for families and one with recipes for early introduction:


Enquiring About Tolerance Study (EAT Study)

- Based on LEAP data, could infants be fed highly allergenic foods earlier and reduce food allergies?
- 1,303 infants 3 months of age exclusively breastfed were assigned to two groups:
  - Standard Practice: Exclusive breastfeeding
  - Introduction Group: Randomly assigned to receive milk, egg, peanut, sesame, whitefish and wheat (2 grams/week)

EAT Results

Food Allergy Prevalence:
- Early introduction group: 2.4%
- Standard introduction group: 7.1%

* Robust for specific foods:
  - Peanut: 0% versus 2.5%
  - Egg: 1.4% versus 5.5%

Not statistically significant, but 67% lower relative risk in food allergies for the early introduction group.

May be food specific

- STAR Trial: randomized controlled trial, 86 participants with moderate-to-severe eczema.
  - Intervention: Egg (egg powder) versus egg avoidance (rice powder) from 4-6 months until 8 months, then introduction and food challenge.
  - Outcome: Small regular amounts of egg from as early as 4 months of age may reduce the incidence of egg allergy.
    - 31% in egg group had allergic reaction to egg powder. Babies may be sensitized by 4 months to egg allergy.
    - 33% that received egg had an egg allergy by 12 months versus 51% that were given rice powder.

Early Introduction

- Other foods do not have official guidance.
- AAP recommends introduction at 6 months to solid foods. Continue breastfeeding.
  "Introduction to solids prior to 4 months is associated with increased weight gain and adiposity, both in infancy and early childhood."
- Feed children the way your Grandparents fed them. Give them tastes from your food.
  - Protection from saliva. Microbiome.
- Consider your population - high risk?
- Peanut intro should be considered in high risk between 7-10 months.
  - Try Bamba - peanut puff
- Encourage families to try regular fruits, vegetables first, then consider allergenic foods.

• STEP Trial: randomized controlled trial, 820 participants with atopic mothers. Babies without eczema.
  - Intervention: Egg versus egg avoidance from 4-6 months until 10 months of age
  - Outcome: Regular egg intake during time period studied does not substantially alter the risk of egg allergy in infants without symptoms of eczema.
Future Treatments for Food Allergies

An exciting future!

Current Research

- 2 Phase III studies underway for peanut allergy treatment
- Mechanisms:
  - Oral
  - Oral plus medication
  - Sublingual
  - Epicutaneous

Will it last?

Tolerance - the goal!
- When child can eat the food without symptoms, despite prolonged periods of avoidance.
- Mechanism: Likely related to initial development of regulatory T-cells and deviation from Th2 response (allergy).

Desensitization
- Protection depends on regular ingestion of food allergen
- Mechanism: Decreased mast cell and basophil reactivity, eventual decrease in food-specific IgE antibodies

Oral Options

- Many small studies have been completed - milk, egg, wheat, peanut, nuts. Sites continue to evaluate efficacy and safety.
- Heating certain foods, like milk and egg make them more tolerable.
- A-Immune PALISADES Trial - Phase III trial ongoing.
  - Multi-center double blind placebo controlled study evaluating use of capsules as home delivery method.
  - Goal is low dose peanut exposure will decrease sensitivity.

Peanut Oral Immunotherapy (OIT)

- Completed phase II study.
  - 79% were able to be desensitized to 443 mg peanut.
  - Those who reached that level were able to go higher upon food challenge.
  - Those who reached 300 mg daily and treated for one year, 80% could tolerate 1 GRAM of peanut at exit food challenges.
- Phase III is underway.

OIT - Heated Protein

- 66%-70% egg allergic children can tolerate baked eggs.
  - Children who reacted to baked milk had higher milk specific IgE antibody levels.
- 75% of milk allergic children can tolerate baked milk.
- Eating baked goods accelerates resolution of egg and milk allergies.
  - We try to encourage patients to complete a baked egg or milk challenge if labs are appropriate.
**OIT + Medicines**

- **Omalizumab (Xolair)**
  - **Rationale:** Improve safety of OIT by decreasing circulating IgE; down-regulate expression of IgE receptor on antigen presenting cells and facilitated antigen presentation.
  - Several studies to be published soon:
    - Single food, such as peanut and milk.
    - Utilize medicine and desensitize to up to 5 allergens at once!

- **Chinese Herbal Medicine**
  - FAHF-1—Contains 11 herbs. Reduced mast cell degranulation, histamine release, peanut specific IgE
  - FAHF-2—9 herbs, potential to block anaphylaxis; showing promise, more research needed

- **Probiotics**
  - Taking along with OIT dose will lessen GI side effects

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**Challenges with OIT**

- Must take every day at home.
- Two hours of inactivity required after dosing
  - Nothing that will increase HR—hot shower, exercise
- Illness, exercise, menstruation and use of NSAIDS may affect.
- 10-20% fail to be orally desensitized.
- Mild-to-moderate mostly oropharyngeal symptoms are common and bothersome to patients.
- 10-20% will develop Eosinophilic Esophagitis (EoE).
- Patients follow anaphylaxis plan at home if symptomatic.

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**Epicutaneous IT**

**Rationale:** Cutaneous exposure to food antigens can re-program T-cells in lymph nodes. In mice, decreased eosinophilia and decreased expression of Th2 cytokines, decreased specific IgE and increased IgG. May decrease the GI side effects of OIT.

**Risk:**
- Lower risk, applied to intact skin.
- No two hours of inactivity with patch placement.

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**Multi-center double blind placebo controlled study evaluating use of patch delivery system.**
- DBV Technologies, Phase Ib & III studies
- Goal is low dose peanut exposure through intact skin will decrease sensitivity.
- Phase Ib Study and follow up study completed May 2016.
  - After 2 years of treatment, about 60% success rate (all ages).
  - In kids 6-11 yrs, 80% able to tolerate 10 x more peanut than started.
- Phase III study underway for children 4-11 yo.
  - Possible future higher dose adolescent/adult patch.

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**EPIT**

**Milk**
- Possible desensitization for IgE allergy to milk.
  - DBV Technologies, MILES, Phase I/II Study underway.
- Proof of concept study underway to evaluate the use in treating EoE with the milk patch.
Sublingual IT

- Administer small drops of allergen extract (mcg-mg milligrams) under the tongue, then eventually spit or swallowed.
  - Doses are approximately 1,000-times less than OIT doses, but SLIT protocols include similar escalation and maintenance dosing.
- Study found 70% responders to peanut SLIT. Those who responded, increased from 3.5 mg to 496 mg after 44 weeks. After 68 weeks, increased to 996 mg (median).
  - Showed it could safely induce a desensitized state in a majority of subjects compared with placebo and that the length of therapy can significantly affect the amount of allergen consumed.

(Nowak-Wegrzyn et al., 2017)

Lessons Learned...

- It is not ready for primetime or clinical care.
  - There are safety issues, risk of reactions... wait until studies are done and FDA review.
  - Some local providers are changing families out of pocket a great deal to perform off label.
  - Caution patients to consider a research study.
- Patients have random reactions. Difficult to predict – can occur outside of exercise, menstruation, NSAID use.
  - Very few actually like the taste.
  - Very individualized - some want to eat the food freely, others want to maintain desensitization.
  - We develop personalized treatment plans after study.
  - High dose daily allergy likely not necessary - low group improved.
  - TIME consuming for families and clinicians.
  - Question data to come post-study participation.
  - Continue daily doses orally for 3-5 years.

References


Emergency Treatment: ABC's

- Airway patency
- Adequate oxygenation
- Recumbent position
- Epinephrine
  - Drug of Choice, Give EARLY!
- Fluids

Supplemental Slides
**Treatment: Skin reactions**

- **Give Diphenhydramine** for hives or mild skin swelling
  - Observe patient as symptoms may progress
- In 12% of allergic reactions, there are no skin findings (and these are typically more severe)

**Treatment: Respiratory tract reactions**

- **Give Epinephrine** for coughing, wheezing, stridor, inability to breathe, and/or airway edema
- **Give Diphenhydramine** for mild symptoms such as rhinitis, sneezing, and nasal congestion
  - If symptoms progress, give epinephrine

**Treatment: GI tract reactions**

- **Give Epinephrine** for repetitive vomiting
- Monitor patient closely if they have abdominal pain, nausea, an episode of vomiting and/or diarrhea

**Treatment for more severe reactions**

- **Give Epinephrine** for:
  - Neurologic — "sense of impending doom"
  - Hypotension
  - Lethargy
  - Shock