Urticaria, Angioedema, Anaphylaxis

Anaphylaxis by 2 mechanisms:

- IgE-mediated
- Non-IgE-mediated
  - Opiates, muscle relaxants, vancomycin, radiocontrast medium
  - NSAIDs (e.g. ibuprofen, naproxen, etc.)
    - Due to IgE & non-IgE-mediated mechanisms

Common Causes:

- Foods:
  - 90% of food-related allergic reactions due to 8 foods (cow’s milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish)
- Drugs:
  - Antibiotics (penicillin, cephalosporins, non-beta-lactams)
Common Causes:

- **Insect venom**
  - Normal reactions: transient, localized pain or itching
  - Large local reaction: marked erythema & swelling that peaks at 24-48 hrs, often involve entire extremity or cross joint, & resolve in 3-10 days with no sequelae
    - IgE-mediated
    - Increased risk for future anaphylaxis with subsequent stings (~5-10%)
    - Tx: symptomatic care. Frequently misdiagnosed (& tx’ed) as cellulitis

- **Latex**
  - up to 75% with spina bifida & 10-15% healthcare workers

- **Vaccines** (0.65 / 1 million doses)
  - Latex in vial stoppers, neomycin, gelatin, egg
  - Egg allergy
    - NOT a contraindication for MMR vaccine
    - Contraindicated: yellow fever vaccine and live intranasal influenza vaccine
    - Injectable single-dose vial influenza vaccine (“Fluzone”) should be given in an allergy/immunology physician’s office with 30 minute observation period.
Acute urticaria

- Acute urticaria (<6 weeks):
  - More likely to have an identifiable etiology than chronic urticaria
  - Viral or bacterial infections: most common cause (> 80%)
    - Particularly in children

- If angioedema with NO urticaria, consider hereditary angioedema:
  - occurs at sites of trauma or around the mouth and extremities
  - +/- preceded by a transient, serpiginous rash
  - +/- abdominal cramping suggesting bowel edema
  - occurs with a family history of similar symptoms
  - requires prolonged treatment
Chronic urticaria

- Recurrent hives on most days of the week for > 6 weeks
- Causes
  - Idiopathic (80-90%)
  - AutoAb vs IgE (30-50%)
  - Physical (~5%)
    - Dermatographism
    - Heat-induced
    - Cold-induced (e.g. to water or air)
    - Delayed-pressure
    - Solar

Does NOT warrant allergy testing

1st line treatment: 2nd generation (long-acting) H₁ antihistamine
Urticaria
Acute urticaria

Dermatographism

Photo courtesy of Dr. Tate Lage
Angioedema
Chronic Urticaria

1st line treatment: 2nd generation (long-acting) H₁ antihistamine
- e.g. cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine
- Effective & better tolerated than 1st generation (short-acting) H₁ antihistamines
- ↓ sedative and anticholinergic effects than older 1st generation H₁ antihistamines
  - E.g. diphenhydramine, hydroxyzine

- 50% to 95% of patients achieve satisfactory disease control ≥1 oral antihistamines

- 1st generation (short-acting) H₁ antihistamines (eg, diphenhydramine, hydroxyzine):
  - Sedation
  - Anticholinergic adverse effects
  - Performance impairment
  - Frequent dosing
  - Paradoxical agitation
  - Inadvertent overdosing
H₂ antihistamines (eg, ranitidine and cimetidine):
- NOT effective monotherapy

Systemic glucocorticoids:
- Effective in controlling symptoms, but symptoms recur as glucocorticoids tapered or discontinued.
- NOT alter the long-term course of the disease

Immunosuppressive medications (steroid-sparing)

Anti-IgE monoclonal Ab (omalizumab, or “Xolair”)
Chronic Urticaria

Other factors to consider:

- Underlying infection
- Autoimmune etiology
  - Fever, weight loss, arthralgias, & other constitutional symptoms
  - Vasculitic
    - Duration of lesions >72 hours
    - Pain
    - Discoloration (Hyperpigmentation)
    - Residual scarring
- Familial pattern/ Hereditary syndromes
- Thyroid disease (Hashimoto, Graves)
- Association with malignant tumor
Anaphylaxis: Diagnosis

Anaphylaxis is highly likely when any 1 of the following 3 criteria fulfilled:

**Criterion 1: Acute onset** of an illness (min to hrs) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND ≥1 OF THE FOLLOWING:

- **Respiratory compromise** (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
- **Reduced BP** or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)
Anaphylaxis is highly likely when any 1 of the following 3 criteria fulfilled:

- **Criterion 2**: \( \geq 2 \) OF THE FOLLOWING that occur rapidly after exposure to a LIKELY allergen for that patient (minutes to several hours):
  
  - Involvement of the **skin-mucosal tissue** (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
  - **Respiratory** compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
  - **Reduced BP**\(^*\) or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)
  - **Persistent GI symptoms** (eg, crampy abdominal pain, vomiting, diarrhea)
Anaphylaxis is highly likely when any 1 of the following 3 criteria fulfilled:

Criterion 3: Reduced BP* after exposure to a KNOWN allergen for that patient (min to hrs):

- **Infants and children** - Low systolic BP (age-specific)* or greater than 30 percent decrease in systolic BP
- **Adults** - Systolic BP <90 mmHg or greater than 30 percent decrease from that person's baseline
Anaphylaxis

- **Frequency of Signs/Symptoms:**
  - Cutaneous (85 – 90%)
  - Upper Airway Angioedema (50-60%)
  - Dyspnea, Wheeze (40 – 50%)
  - Dizziness, Syncope, Hypotension (30-35%)
  - Abdominal (25-30%)

- Prior episodes of anaphylaxis do not predict future episodes of anaphylaxis.
A 2-year-old girl presented to the urgent care center for rash and swelling of her lips.

While visiting a neighbor, the girl took a few bites of a peanut butter cracker and started coughing.

The mother initially thought that her daughter had choked on the cracker, but then noticed that the girl had developed hives on her face.

The mother wiped her daughter’s face and mouth and gave her a teaspoon of diphenhydramine.

The hives began to fade, but the girl then developed lip swelling and a raspy voice. She became progressively irritable and now appears to be breathing fast.
Question 1

Of the following, the MOST appropriate step in this girl’s management is to administer

A. injectable corticosteroid
B. injectable epinephrine
C. nebulized albuterol
D. ranitidine and diphenhydramine
E. scheduled diphenhydramine
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Resolution of anaphylaxis may occur in:
- Uniphasic: min to hours
- Biphasic
  - Recurrence after initial improvement of symptoms
  - ~20% experience 2-24 hrs after initial reaction
- Protracted resolution

Epinephrine: administer promptly at the onset of symptoms suggestive of anaphylaxis

Epinephrine is life-saving:
- $\alpha$-adrenergic vasoconstrictor effects in most body organ systems
- Prevent and relieve airway obstruction
- $\beta$-adrenergic inotropic and chronotropic properties on the heart
- Decrease mediator release from mast cells
Anaphylaxis: Treatment

- **2nd line treatment options in the outpatient setting:**
  - Antihistamines
  - β₂-agonists
  - Glucocorticoids

- **Antihistamines** (both \( H_1 \) and \( H_2 \) blockers)
  - Should **NEVER** be used alone for anaphylaxis treatment
  - Given **AFTER** epinephrine administration

- **Glucocorticoids**
  - Potential to prevent the biphasic reaction & recurrent/protracted anaphylaxis

- **β₂-agonists** (inhaled albuterol)
  - Can improve bronchospasm
  - **NOT** alter the course of the reaction
Anaphylaxis: Treatment

1) Epinephrine: initial/immediate medication
   • 0.01 mg/kg (maximum initial dose: 0.5 mg)
   • Current epinephrine injectors are available in 2 strengths (doses):
     0.15 mg and 0.30 mg
   • 10-20% of pts may require 2nd dose epinephrine

2) CALL 911 for EMS transport to ER!

3) H1 oral antihistamines (e.g. Benadryl)

4) Albuterol - if history of asthma
   • Corticosteroid
   • H2 oral antihistamine
   • Rx: EpiPen 2-pack
     • May require 2nd dose epinephrine in 5-10 min after 1st dose
     • Education - indications & technique
**FOOD ALLERGY & ANAPHYLAXIS EMERGENCY CARE PLAN**

**EXTREMELY REACTIVE TO THE FOLLOWING FOODS:**

**THEREFORE:**
- [ ] If checked, give epinephrine immediately for ANY symptoms if the allergen was likely eaten.
- [ ] If checked, give epinephrine immediately if the allergen was definitely eaten, even if no symptoms are noted.

### FOR ANY OF THE FOLLOWING:

#### SEVERE SYMPTOMS

- **LUNG**
  - Short of breath, wheezing, repetitive cough

- **HEART**
  - Pale, blue, fast, weak pulse, dizzy

- **THROAT**
  - Tight, hoarse, trouble breathing/swallowing

- **SKIN**
  - Rash, hives, itching, hives rash, hives rash

- **GUT**
  - Repetitive vomiting, severe diarrhea

- **OTHER**
  - Feeling something bad is about to happen, anxiety, confusion

### MILD SYMPTOMS

- **NOSE**
  - Itchy, scratchy nose, sneezing

- **MOUTH**
  - Itchy mouth, mouth, lips, tongue

- **SKIN**
  - A few hives, mild itch, discomfort

- **GUT**
  - Mild nausea, discomfort

**FOR MILD SYMPTOMS FROM MORE THAN ONE SYSTEM AREA, GIVE EPINEPHRINE.**

**FOR MILD SYMPTOMS FROM A SINGLE SYSTEM AREA, FOLLOW THE DIRECTIONS BELOW:**

1. Antihistamines may be given, if ordered by a healthcare provider.
2. Stay with the person; alert emergency contacts.
3. Watch closely for changes. If symptoms worsen, give epinephrine.

### MEDICATIONS/DOSES

- **Epinephrine Brand:**
  - [ ] 0.15 mg/mL
  - [ ] 0.3 mg/mL

- **Epinephrine Dose:**
  - [ ] 0.15 mg/mL
  - [ ] 0.3 mg/mL

- **Antihistamine Brand or Generic:**
  - [ ]

- **Antihistamine Dose:**
  - [ ]

- **Other (e.g., inhaler, bronchodilator, if allergic):**
  - [ ]
Food Allergy

- Food allergy:
  - Most common cause of anaphylaxis in home or school setting
  - 50% of all pediatric cases of anaphylaxis annually
  - 85% to 90% of allergic reactions to food in children – due to the 8 most common food allergens:
    - milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish
# Food Allergy

<table>
<thead>
<tr>
<th>Infants and Children</th>
<th>Adolescents and Adults</th>
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<tbody>
<tr>
<td>Milk</td>
<td>Peanut</td>
</tr>
<tr>
<td>Egg</td>
<td>Tree nut</td>
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<tr>
<td>Soy</td>
<td>Fish</td>
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<td>Wheat</td>
<td>Shellfish</td>
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<tr>
<td>Peanut</td>
<td></td>
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<tr>
<td>Tree nut</td>
<td></td>
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<tr>
<td>Fish</td>
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</tbody>
</table>
> 90% of food-allergic individuals demonstrate clinical responses to only 1 or 2 foods

Peanut allergy
- ≤ 50% of children with peanut allergy may develop tree nut allergies

In westernized countries:
- Milk allergy: most common food allergen in infants (2.5%)
- Egg allergy (1.5%)
Food Allergies & Atopic Dermatitis

- National Institute of Allergy and Infectious Diseases (NIAID) food allergy guidelines recommend children <5yo with moderate to severe atopic dermatitis (AD) be considered for food allergy evaluation for milk, egg, wheat, soy, and nuts, if at least 1 of the following conditions is met:
  
  (a) **persistent AD despite optimized management and topical therapy**
  OR
  
  (b) **reliable history of an immediate reaction after ingestion of a specific food**

- ~30% to 40% of infants with moderate-to-severe AD may have an underlying IgE-mediated food allergy exacerbating the AD and should undergo food allergy testing
Diagnosis & Treatment of Allergic Disease: Skin testing

- Allergy skin testing: more sensitive & specific than blood testing

- Indications for immediate-type skin testing
  - Identification of aeroallergen triggers in patients who have asthma
    - ~ 60% of children with persistent asthma have coexisting allergic rhinitis
  - Allergic rhinitis that is not controlled with usual medications or if allergen avoidance is desired
    - Allergies to seasonal environmental allergens typically do not develop until ≥3 years of age.
  - Food allergy
  - Insect sting allergy
  - Vaccine, drug, or latex allergy
  - Evaluation for moderate-to-severe atopic dermatitis
  - Other conditions: allergic fungal sinusitis, allergic bronchopulmonary aspergillosis, and eosinophilic esophagitis

** Discontinue oral antihistamines 5 days prior to initial evaluation.
** Skin testing may only be performed ≥6 weeks from anaphylaxis.
Clinicians who obtain specific IgE to a specific allergen should be comfortable with interpretation and application of test results for specific clinical scenarios.

Age-specific IgE values are utilized in interpretation of the most common food allergens – *not* class I-V as included in interpretation of many commercial lab results.

Do NOT recommend obtain serum specific IgE values for foods prior to allergy/immunology evaluation.
Pediatric Allergy/Immunology

- Food allergy
- Anaphylaxis
- Angioedema
- Allergic rhinitis ("seasonal allergies", "hayfever")
- Insect venom allergy
- Drug allergy
- Eczema, or atopic dermatitis
- Eosinophilia, Hypereosinophilic syndrome
- Systemic mastocytosis
- FPIES (food-protein induced enterocolitis)
- Eosinophilic esophagitis
- Hereditary angioedema
- Asthma (**NOT** other pulmonary diagnoses)
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

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<table>
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<tbody>
<tr>
<td>1</td>
<td>Four or more new ear infections within 1 year.</td>
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<tr>
<td>2</td>
<td>Two or more serious sinus infections within 1 year.</td>
</tr>
<tr>
<td>3</td>
<td>Two or more months on antibiotics with little effect.</td>
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<tr>
<td>4</td>
<td>Two or more pneumonias within 1 year.</td>
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<tr>
<td>5</td>
<td>Failure of an infant to gain weight or grow normally.</td>
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<tr>
<td>6</td>
<td>Recurrent, deep skin or organ abscesses.</td>
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<tr>
<td>7</td>
<td>Persistent thrush in mouth or fungal infection on skin.</td>
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<tr>
<td>8</td>
<td>Need for intravenous antibiotics to clear infections.</td>
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<tr>
<td>9</td>
<td>Two or more deep-seated infections including septicemia.</td>
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<tr>
<td>10</td>
<td>A family history of PI.</td>
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Primary Immunodeficiency –
Indications for Immune Evaluation

- Recurrent/severe cutaneous viral infections (e.g. HSV, molluscum, warts, HPV, etc.)
- Recurrent or severe abscess or cellulitis
- Mastoiditis
- Liver, splenic, or lung abscess
- Osteomyelitis
- Sepsis, Bacteremia
- Meningitis
- Recurrent or chronic sinusitis
- Hepatosplenomegaly or lymphadenopathy
- Cytopenias – especially in addition to severe or recurrent infections
- Severe atopic dermatitis – especially in addition to severe/recurrent infections
- Bronchiectasis
- Chronic diarrhea
Pediatric Allergy/Immunology

- Recurrent, severe, or opportunistic infections
- Low IgG, IgA, or IgM, or hypogammaglobulinemia
- Lymphopenia
- Primary immunodeficiency diseases
  - Severe combined immunodeficiency disease (SCID)
  - 22q11.2 deletion syndrome, or DiGeorge syndrome
  - Chronic granulomatous disease (CGD)
  - Ataxia-telangiectasia
  - Hyper IgE syndrome (e.g. Job syndrome)
  - Hyper IgM syndrome
  - Common variable immunodeficiency disease (CVID)
  - X-linked agammaglobulinemia (“Bruton’s agammaglobulinemia”)
  - Leukocyte adhesion deficiency
  - Autoimmune lymphoproliferative syndrome (ALPS)
“Bubble Boy” (David Vetter)
Thank you!