Pediatric Board Review
Allergy & Immunology

David J. Resnick, M.D.
Director, Division of Allergy
The New York Presbyterian Hospital
Goal of Talk

Identify common pediatric allergic diseases
Learn to diagnose and manage these conditions
Discuss the presentation and diagnoses of primary immunodeficiencies
Ninety percent of the audience will be awake at the end of the talk
Pathophysiology of Sensitization to Allergen

Allergen → Antigen-Presenting Cell → Processed Allergen → HLA Class II → CD4\(^+\) Th\(_2\) Cell

CD4\(^+\) Th\(_2\) Cell → IL-4 → B Cell → IL-13 → Plasma Cell → IgE Antibodies → Sensitized Mast Cell

HLA = human leukocyte antigen; IgE = immunoglobulin E.
Late-phase reaction

Hyperresponsiveness

Priming

Resolution

Irreversible disease

Early Inflammation

Late Inflammation

Mast cell

Mediator release

Cellular infiltration

Eosinophils
Basophils
Monocytes
Lymphocytes

Blood vessels

Nerves
Glands

Sneezing
Rhinorrhea
Congestion
Mast Cell

- Histamine
- Leukotrienes
- PAF
- Prostaglandins
- ECF
- NCF
Eosinophil

PAF
LTC4
Major Basic Protein
Cationic Protein
Immediate and Late Reactions in IgE-mediated Hypersensitivity

**Immediate Reactions**

**Late Reactions**

**STEP 1**
Sensitization

**STEP 2**
Early Phase
Minutes (A)

**STEP 3**
Late Phase
Hours (B)
Gell and Coombs
Allergic Mechanisms

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen</td>
<td>Complement</td>
<td>Antigen</td>
<td>Macrophage</td>
</tr>
<tr>
<td>IgE</td>
<td>Antibody</td>
<td>Antibody</td>
<td></td>
</tr>
<tr>
<td>Mast cell</td>
<td>Antibody</td>
<td>Polymorphonuclear leukocyte</td>
<td></td>
</tr>
<tr>
<td>Mediator release</td>
<td>Red cell</td>
<td></td>
<td>T-cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cytokines</td>
</tr>
</tbody>
</table>

[Diagram showing different allergic mechanisms]
Classification of Allergic Diseases

- **Type I** – allergic rhinitis/conjunctivitis, allergic asthma, anaphylaxis, drug reactions, latex allergies, venom allergies, seminal plasma protein allergies, hives, food allergies
- **Type II** – autoimmune hemolytic anemia
- **Type III** – serum sickness (PCN, Ceclor)
- **Type IV** – contact dermatitis (chemicals in latex gloves, latex, poison ivy, nickel)
- **Other** – direct mast cell release
An 18 yr old presents with hives, pruritis, SOB, after eating at a seafood restaurant. There is a history of a shrimp allergy but he ordered tuna. His BP is 120/70, Oxygen sat was 92% on RA. The most appropriate action is to:

1. Administer SC Epinephrine
2. Administer IM Benadryl
3. Administer PO Benadryl
4. Administer IM Benadryl and send an Immunocap for Tuna
5. **Administer IM Epinephrine**
Signs & Symptoms of Anaphylaxis

- **Respiratory** - hoarseness, dysphagia, cough, wheezing, SOB, tightness in throat, rhinorrhea, sneezing
- **Cardiovascular** - faintness, syncope, arrhythmia, hypotension
- **Skin** - flushing, pruritus, urticaria angioedema,
- **Gastrointestinal** - nausea, abdominal pain, vomiting, diarrhea
- **Mouth** - edema & pruritus of lips tongue and palate
- **Other sites** - uterine contractions, conjunctival edema, feeling of impending doom
Triggers of Anaphylaxis

- **Foods** - children: peanuts, nuts, fish, shellfish
  infants: milk, eggs, wheat, soy
  (contamination commonly happens at restaurants)

- **Medications** - penicillin & derivatives, cephalosporins, tetracycline, sulfonamides, insulin, ibuprofen

- **Allergen vaccines**

- **Latex**

- **Insect Venom**

- **IV contrast material** (Anaphylactoid Reaction)
Acute Treatment of Anaphylaxis

IM Epinephrine is the first line therapy for Anaphylaxis. This is almost always the answer to anaphylaxis on Board questions.

- Early recognition and treatment
  - delays in therapy are associated with fatalities
- Assessing the nature and severity of the reaction
- Brief history
  - identify allergen if possible
    - initiate steps to reduce further absorption
- General Therapy
  - supplemental oxygen, IVF, vital signs, cardiac monitoring
- Goals of therapy
  - ABC’s
Tx Anaphylaxis 2

- Oxygen
- Benadryl IM 1mg/kg
- Steroids
- IV fluids
- Nebulized albuterol
- H2 blockers
- Epinephrine/Dopamine/Norepinephrine
Differential Diagnosis of Anaphylaxis

- Vasovagal - hypotension, pallor, bradycardia, diaphoresis, no hives or flushing
- Scombroidosis – hives, headache, nausea, vomiting, Klebsiella & Proteus produce saurine (Spoiled Mackerel, Tuna)
- Carcinoid – flushing, diarrhea, GI pain,
- MSG – flushing, burning, chest pain, headache
- Angioneurotic edema Hereditary/Acquired
- Panic attacks
- Systemic mastocytosis- mastocytomas
A 10 year old presents with an insect sting that occurred yesterday and now has redness and swelling localized to the arm where he was stung. The redness extended to the entire forearm. There is no fever, chills, SOB or any generalized response.

This reaction is best characterized by:

A) Cellulitis
B) Large local reaction
C) Normal reaction
D) Anaphylaxis
E) Toxic reaction
A 5 year old presents with hives, SOB, dizziness, and drop in BP, after being stung by an insect. Which of the following statements is true:

- 1) Epinephrine SC is the treatment of choice
- 2) The chance of having another anaphylactic reaction to a similar sting is 10%
- 3) This patient needs immunotherapy
- 4) IV Epi should be given
- 5) Get an allergy consult to perform testing to determine what stung him
Classification of Insect Reactions

- Immediate - within 2-4 hours
  - Local reactions - swelling and erythema extending from the insect bite *(no antibiotic tx)*
  - Systemic reactions - are generalized and involve signs and symptoms at a site remote from the sting

- Delayed reactions - can occur days later
  - Swelling and erythema
  - Serum sickness - fever, hives, lymphadenopathy
  - Guillain-Barre syndrome
  - Glomerulonephritis
  - Myocarditis
  - Fever, myalgia, and shaking chills between 8-24 hrs. post sting
Toxic reactions

- Usually results from multiple simultaneous stings
- Similar clinical characteristics of anaphylaxis
- Differentiation between a toxic reaction and anaphylaxis may be difficult
- Some patients may develop IgE antibodies after a toxic reactions and may be at risk for developing an allergic reaction to subsequent stings
- Reaction is probably due to vasodilation from chemicals of the sting
## Indications for Venom IT

<table>
<thead>
<tr>
<th>Reaction to sting</th>
<th>Venom Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anaphylaxis (More than cutaneous reaction)</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cutaneous eruptions</strong></td>
<td></td>
</tr>
<tr>
<td>Age 15 and younger</td>
<td>No</td>
</tr>
<tr>
<td>Older than 15</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Large local reaction</strong></td>
<td>Not required but increased chance of anaphylaxis</td>
</tr>
<tr>
<td><strong>Normal Reactions</strong></td>
<td>No</td>
</tr>
</tbody>
</table>
A 10 yr old presents with a 1 yr hx of abdominal pain, bloating, diarrhea I hr after eating dairy. PE normal and negative guaiac. The most likely cause of his symptoms is

1. Oral allergy syndrome
2. Milk protein allergy
3. Allergic eosinophilic gastroenteritis
4. **Lactose intolerance**
5. Milk protein enterocolitis
Facts to know

• IgE milk allergies usually begin in the 1st year of life- hives, AD, & anaphylaxis within minutes to an hr of ingestion
• Milk protein enteropathies usually present within the 1st year of life with hematochezia, diarrhea, & vomiting
• Oral allergy is due to fruits & is associated with pollen allergies
• EE we’ll talk about later
• Lactase deficiencies usually present after 6 yrs of age- bloating
An 8 yr old presents with fever, arthralgia, arthritis and urticaria 3 days after completing a course of amoxicillin for strep throat. The most likely diagnosis is:

1. **1) serum sickness**
2. 2) IgE mediated pcn allergy
3. 3) post streptococcal arthritis
4. 4) erythema multiforme
5. 5) delayed PCN allergy
Facts to know

- EM classically have target lesions
- IgE mediated medication reactions usually start within a few days after initiating therapy
- Serum sickness is type III reaction that begins 1-2 wks (up to 20 days) from initiating therapy. Fever, rash, malaise, lymphadenopathy, arthralgia & arthritis
A 7 year old girl had a history of URI symptoms & fever 2 weeks ago and was given OTC medications. She also ingested broccoli for the first time. She has had this rash for 2 weeks.
The most likely cause of this rash is:

1. a viral infection
2. a dye in her OTC medication
3. Ibuprofen
4. Lyme disease
5. allergy to broccoli
Etiology of Hives

- **Foods**: children - peanuts, nuts, fish, shellfish; infants - milk, eggs, wheat, soy (contamination commonly happens at restaurants)
- **Medications**: penicillin & derivatives, cephalosporins, tetracycline, sulfonamides, insulin, ibuprofen
- **Viral infections**: can last weeks as opposed to foods
- **Physical urticarias**: dermographism, pressure, cold, heat, solar, exercise, vibratory
- **Idiopathic
- **Medical conditions are unlikely to trigger hives in the pediatric population**
A ten year old presents with recurrent angioedema of the extremities and at times his throat. His past medical history is significant for surgery to R/O appendicitis but no clear diagnosis was made. The family Hx is significant for a father with a peanut and PCN allergy. The most appropriate test to perform is:

1. Peanut Rast
2. **C4 level**
3. Skin testing for PCN
4. SPEP
5. C1 level

![Bar chart showing percentages for each option.](chart.png)
Hereditary Angioneurotic Edema (HAE)

- Patients do not have Hives with attacks
- Usually present from 3-20 years of age
- Often is discovered after the patient presents with symptoms of appendicitis
- **C1 esterase inhibitor** is deficient causing increase in kinins and edema
- **C4 is almost always low**, C2 is low during attacks
- C1 esterase inhibitor levels are low but there is a version with normal levels but abnormal functioning
- Treatment with C1 esterase inhibitor and other therapies are now available
A 13 yr old presents with hives for 6 months. He had Immunocap testing performed which was positive for dust mites, milk and shrimp. The hives last 3-5 hours, then disappear.

• The most likely cause of the hives is:
• A) autoimmune thyroid disease
• B) allergies to dust
• C) allergies to food
• D) mastocytosis
• E) autoantibodies to the IgE receptor
Facts to know

• Chronic urticaria is defined by hives lasting more than 6 weeks. It is rarely caused by foods or inhalants. Positive Immunocap testing usually means very little with hives unless there is a clear history suggesting a cause.

• Routine Immunocap testing for chronic hives is not indicated.

• CU in 40% of patients is caused by autoantibodies to the IgE Fc epsilon 1 receptor

• Thyroid antibodies are associated with CU but is not the cause
A 4 yr old presents with sneezing and rhinorrhea lasting 4 days. The discharge is from one nostril, foul smelling and is described as blood tinged.

The most likely diagnosis is

A) Allergic rhinitis
B) Sinusitis
C) Nasal foreign body
D) Nasal polyps
E) Viral rhinitis
A three year old presents with recurrent respiratory infections, chronic rhinitis that is bilateral & year round. Your examination of the nose reveals these pictures.
Continued

• The most likely diagnosis is

• A) granuloma
• B) cystic fibrosis
• C) deviated septum
• D) foreign body
• E) Bruton's agammaglobulinemia
A 7 year old presents with a 3 year history of seasonal rhinorrhea and congestion. His symptoms begin each spring. On PE you note pale boggy turbinates and a transverse nasal crease.
The most effective long term treatment is a nasal spray containing a

- A) corticosteroid
- B) anticholinergic
- C) decongestant
- D) mast cell stabilizer
- E) saline solution
• Topical nasal steroids are the most potent treatment for allergic rhinitis
• Anticholinergic nasal sprays may help for vasomotor rhinitis/non allergic rhinitis
• Mast cell stabilizers must be used several times a day for many days before it starts working
• Nasal decongestant can cause a rebound effect when used more than 5 days
Signs and Symptoms of Allergic Rhinitis

- Sneezing
- Itchy nose, eyes, throat, and/or ears
- Nasal congestion
- Clear rhinorrhea

- Conjunctival edema, itching, tearing, hyperemia
- Subocular edema and darkening ("shiners")
- Loss of taste and smell sensations
- Diagnosis depends on a thorough patient history regarding symptoms suffered, seasonal and/or perennial patterns of symptoms, and symptom triggers
- Diagnosis is confirmed by allergy skin testing or RAST
# Differential Dx of Rhinitis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor rhinitis</td>
<td>congestion, rhinorrhea</td>
</tr>
<tr>
<td>Anatomical</td>
<td></td>
</tr>
<tr>
<td>Adenoidal hypertrophy</td>
<td>congestion, snoring</td>
</tr>
<tr>
<td>Deviated septum</td>
<td></td>
</tr>
<tr>
<td>Polyps</td>
<td>must R/O CF</td>
</tr>
<tr>
<td>Foreign body</td>
<td>unilateral, bloody or brown discharge</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>clear rhinorrhea</td>
</tr>
<tr>
<td>sinusitis</td>
<td>mucopurulent discharge, cough, facial pain, tooth pain</td>
</tr>
</tbody>
</table>

(Most common symptom of chronic sinusitis is chronic cough)
Differential Dx 2

Diagnosis

• Hormonal
  – Pregnancy, hypothyroidism
• CSF fluid – *cribiform plate* Fx, MVA
• Rhinitis medicamentosa
  – Beta blockers, cocaine
  – OTC nasal sprays (AFRIN)

Symptoms

  – congestion
  – clear rhinorrhea
  – congestion rhinorrhea
  – rebound congestion
A 6 year old boy has increased symptoms of asthma each fall when school begins. He also experiences rhinorrhea, congestion and ocular symptoms during this time.

• The most likely trigger to his symptoms are
  • A) sinusitis
  • B) GE reflux
  • C) viral infections
  • D) allergic rhinitis
  • E) school stress
What allergens trigger Rhinitis & Asthma?

- Indoor allergens (cause year round symptoms)
  - Dust mites (avoidance measures)
  - Mold
  - Cockroaches
  - Pets – cats, dogs, rats, mice, guinea pigs, & birds

- Outdoor allergens (cause seasonal symptoms)
  - Pollen – trees, grass, weeds
  - Molds
  - Animals – horses, cows
Asthma Triggers

• Eighty percent of children with asthma develop allergic rhinitis, a known trigger to asthma
• GER exacerbates asthma and can be silent. Most infants will have frequent spitting up or vomiting. Older children can complain of heartburn
• School stress can result in a psychogenic cough (disappears when sleeping)
• Sinusitis also exacerbates asthma and would be suspected with a purulent discharge
• URI’s are the most common trigger in infants
• Exercise in the school age child triggers symptoms in most asthmatics
The risk factor most associated with fatal asthma is

- A) Poor perception of asthma
- B) high socioeconomic status
- C) female
- D) sinusitis
- E) Inhaled steroid use
• Risk factors for near fatal and fatal asthma include frequent visits to the ER, hospitalizations, psychosocial disturbances, male sex, poor perception of hypoxia, low socioeconomic status, over use of beta agonists
An allergic inner city 10 year old child has perennial rhinitis and asthma. The most common allergen responsible for this inner city asthmatic is

- A) Cockroach
- B) Cat dander
- C) Dust mites
- D) Mouse urine
- E) House dust
• 2 month old boy presents with blood in the stools. Started 3 weeks ago. FT, NSVD, no complications. Breastfeeding since birth with supplementation. Initially on cow’s milk formula, but switched to soy-based formula when blood was noticed in the stool. Symptoms continued so switched to extensively hydrolyzed formula.

• What is the diagnosis?
• What is the management?
Dietary protein induced proctocolitis syndrome

- Affects children in first few months of life
- Symptoms: blood streaks mixed with mucus in stools, no systemic symptoms
  - Minimal blood loss, anemia is rare
- Milk is the most common cause, soy can be another trigger (50% of milk allergic pts are also soy allergic)
- Non IgE mediated reaction
- Tx – Avoidance- Most outgrow the allergy between 1-2 yrs

Sicherer, Pediatrics 2003
The following is true concerning food allergies:

A) The AAP recommends allergic infants be breastfed or given a hydrolyzed formula for the first 6 months of life
B) The AAP recommends delaying peanut exposure until 2 years of age
C) The AAP recommends delaying peanut exposure until 3 years of age
D) The AAP recommends mothers avoid allergic foods while pregnant
E) The AAP recommends mothers avoid allergic foods while nursing
A 5 yr old has a hx of a peanut allergy. Skin prick testing confirmed the allergy. The mother asked about the child’s risk of other food allergies. The food most likely to cause an allergic reaction is

- A) wheat
- B) beans
- C) shrimp
- D) fish
- E) tree nuts
A 1 yr old presents with severe gastroesophageal reflux that failed tx with multiple medications. She had a Nissen fundoplication and continues to reflux. Biopsy of the esophagus showed eosinophils. The following is true except:

A) There should be greater than 20 eosinophils per high power field on the biopsy
B) Exclusive feeding with an amino based formula usually resolves the problem
C) Inhaled steroids that are swallowed helps this condition
D) The most common food that causes this condition is soy
E) Antihistamines in general don’t work for this condition
When to consider an immunodeficiency

Unusual infections (recurrent and severe) – abscess, pneumonia, sinusitis, thrush
Unusual bugs
Antibiotics don’t help, need IV antibiotics
Failure to thrive
Family history of immunodeficiency

What is a normal number of infections?
Usually 6-8 colds per year
Children attending daycare or have siblings in school tend to have more than others
Not unusual to have 6 otitis or 2 gastroenteritis in first few years
The Immune System

- T cells
- B cells (that make immunoglobulins)
- Phagocytic system (neutrophils and macrophages)
- Complement
A 2 year old presents with recurrent bacterial and viral infections. The most appropriate initial tests to be performed are:

- A) immunoglobulin subsets
- B) candida and tetanus skin tests
- C) B & T cell subsets
- D) complement 50 assay
- E) CBC and immunoglobulins
Work up of Immunodeficiencies

• 70% of Immunodeficiency syndromes have immunoglobulins that are abnormal

• CBC with differential allows us to look at neutrophil & lymphocyte count, and platelets
B cell Work Up

- CBC with diff
- Quantitative Immunoglobulins
- Pre & Post vaccination titers
- Isohemmaglutinin testing (antibodies to AB blood antigens)
Work up of Immunodeficiencies

• T cell- Cell mediated immunity – delayed type hypersensitivity intradermal skin test candida, tetanus, mumps, trichophyton. Other measures include lymphocyte count, T cell subpopulations by flow cytometry and lymphocyte stimulation tests

• Dihydrorhomadine fluorescence (DHR 123) measure neutrophil respiratory burst and is replacing the NBT test that diagnoses Chronic Granulomatous disease
Work up of Immunodeficiencies

- Complement deficiencies only make up 2% of primary immunodeficiencies
- Total Complement assay (complement 50 or CH 50) measures the intactness of the classic complement pathway. Deficiencies from C1 through C9 can be picked up with this test
Primary Immune System Defects
Present With

- T cells – viral & fungal infections
- B cells – recurrent bacterial infections
- Phagocytic system- cellulitis, skin abscesses, pneumonia, periodontal disease
- Complement- c5-9 Neisserial infections
  C1,2 & 4 - recurrent bacterial infections & SLE
A 14 month old presents with severe eczema, recurrent otitis, Strep Pneumo pneumonias. Blood tests reveal thrombocytopenia and small platelets.

The most likely diagnosis is:

- A) X linked severe combined immunodeficiency
- B) DiGeorge syndrome
- C) Wiskott-Aldrich syndrome
- D) Chronic granulomatous disease
- E) Brutons X linked agammaglobulinemia
Wiskott-Aldrich syndrome

- Prolonged bleeding after circumcision, bloody diarrhea
- Recurrent infections and significant eczema that begin prior to 1 year of age
- Small platelets and Thrombocytopenia
- Treatment- IV gammaglobulin, prophylactic antibiotics, Identical bone marrow transplant
Brutons X linked agammaglobulinemia

- Defect in the B cell tyrosine kinase protein
- Decrease in B cells production
- Severe hypogammaglobulinemia
- Small or absent tonsils
- Sinopulmonary infections after 6 months of age
- Tx – IVIG
CVID - Common variable immunodeficiency

Similar presentation to Brutons (sinopulmonary infections) but occurs in the older child or adult

Not as severe hypogammaglobulinemia as Brutons

Diarrhea due to Giardia

Normal B cells

Tx - IVIG
Chronic Granulomatous Disease (CGD)

- Disorder of phagocytic system
- Inability to kill catalase positive organisms (Staph aureus, Serratia, Burkholderia cepacia, Salmonella, Aspergillus, & Candida)
- Recurrent lymphadenitis, skin infections, hepatic abscesses & osteomyelitis
- Tx - Cure – bone marrow transplant
  - Supportive care- interferon gamma and prophylactic antibiotics

Diagnosis DHR 123 or NBT test
DiGeorge Syndrome

- Genetic disorder linked to chromosome 22 q11.2 & dysmorphogenesis of the 3\textsuperscript{rd} and 4\textsuperscript{th} pharyngael pouches
- Can have a partial or complete DiGeorge
- Can present in infancy with hypocalcemic tetany
- Aortic arch and cardiac defects
- Hypoplastic mandible, defective ears, and a short philtrum, absent thymus
- Recurrent viral, bacterial and fungal infections
- Tx- Bone marrow or thymic transplant
Ataxia Telangiectasia

- Telangiectsis of conjuntivae and skin
- Cerebellar degeneration and ataxia
- Dysarthria, nystagmus, choreoathetosis
- Recurrent sinus, ear, and pulmonary infections
- Decrease in IgA & IgE
- Low lymphocyte count with poor mitogen stimulation response
- Abnormal delayed type hypersensitivity
SCID (severe combined immunodeficiency)
T and B cells defects

- **Onset in early life**
- Medical emergency
- Recurrent sepsis, pneumonia, otitis, rash, diarrhea
- Opportunistic infections – PCP, Candida
- FTT when infections begin
- Severe lymphopenia – no lymphoid tissue, no thymus
- Death by age 2 years
- Treatment: stem cell transplant
- Many different mutations
Transient Hypogammaglobulinemia of Infancy

- All children need several years for immunoglobulins levels and antibody responses to become normal
- Small number of children with recurrent infections have been found to have low immunoglobulin levels that eventually normalize
- Have ability to form specific antibodies in response to immunizations
- Have normal immunoglobulin levels by 2-4 years
- Need to compare levels based on age – some lab reference ranges are adult levels
Leukocyte adhesion defect (LAD)

- Delayed separation of umbilical cord
- Elevated WBC count
- Recurrent necrotic infections of skin, mucous membranes, GI tract

- 2 types
  - LAD-1 – defect or deficiency in CD18
  - LAD-2 – defect in fucose metabolism (rare)