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Disclosure: None
Upon completion of this session, participants should be able to understand, recognize and manage the following conditions:

- **Common allergic diseases in children**
  - Allergic Rhinoconjunctivitis
  - Atopic dermatitis
  - Food allergy

- **Common primary Immunodeficiency**

- **Common rheumatologic diseases in children**
  - Acute arthritis: ARF, reactive arthritis, Transient toxic synovitis,
  - Chronic arthritis: JRA (JIA)
Atopy and Atopic Diseases

- Atopy: A genetically predisposed diathesis manifesting as exaggerated responses (e.g., bronchoconstriction, IgE production, vasodilation, pruritus) to a variety of environmental stimuli (irritants, allergens, and microbes).

- Atopy is fundamental to the pathogenesis of atopic allergic diseases; allergic rhinoconjunctivitis, asthma, food allergy, atopic dermatitis.

- Not every atopic child develops atopic diseases.
- Not every child with atopic disease is atopy.
Atopy and Atopic Diseases

• Objective evidence of being atopy:
  – Elevated total IgE in serum for age
  – Specific IgE to specific allergens:
    • *In vivo*: Specific IgE on mast cells (skin)
      – Prick skin test
      – Intradermal skin test
    • *In vitro*: Specific IgE in serum
      – Radioallergosorbent test (RAST)
      – Fluoreszymeimmunoassay (ImmunoCAP)

Limitation of the specific IgE tests
• The positive result does not predict the severity of the reaction.
• The positive result does not directly inform the patient’s symptoms caused by the allergen.
Allergic March

Sensitization to allergens

+/- -- 3-48 months

+/- 4-36 months

+/- 8-48 months

++ 4-12 years

+++ 9-14 years

+/- >25 years

Food-related allergy symptoms

Wheeze

Asthma

Rhinitis

Eczema

Adult allergic asthma or rhinitis

Wickman Allergy 2005
Allergic March

Barnestson RS and Rogers M, *BMLJ* 2002
Key Components of Allergic Diseases

• Allergen:
  – Allergens: size 10-70kD
  – Indoor/ outdoor allergens, season, foods etc.

• Allergen exposure:
  – Major organs: Eye, upper/lower respiratory tract, GI, skin
  – Most of symptoms related to mediators from mast cell degranulation and eosinophilic inflammation.

• Family History:
  – Risk 50% if one parent is allergic
  – Risk 66% if both parents are allergic
A 9 month old infant with on and off itching skin rash since 3 months of age. The rash previously responded to hydrocortisone. 

Which one is the most likely diagnosis?

A. Atopic dermatitis  
B. Seborrheic dermatitis  
C. Contact dermatitis  
D. Scabies  
E. Psoriasis
Atopic Dermatitis

- Chronic inflammatory pruritic skin disease characterized by a relapsing course with broad clinical presentation from minimal fleural eczema to erythroderma.
- 45% of children AD in the first 6 months
- 15% of children in US.
- 4% of all ED visit
- Often complicated by secondary skin infections
Atopic Dermatitis

Nomenclature: Neurodermatitis, atopic dermatitis, eczema

1. **Atopic eczema** is associated with IgE-mediated sensitization and typifies 70–80% of AD patients.

2. **Non-atopic eczema** is not associated with IgE-mediated sensitization seen in 20–30% of AD patients.

Both are associated with eosinophilia

Eczema family
- Atopic dermatitis (AD)
- Seborrheic dermatitis
- Contact dermatitis
- Nummular eczema
- Xerotic (asteatotic eczema)
- Ids (dermatophytids)
- Dyshidrotic eczema
- Autoeczematization
- Lichen simplex chronicus
- Prelymphomatous

Leung, Nelson textbook of pediatric 18th ed
Simpson & Hanifin, Med Clin N Am 2006
Atopic Dermatitis

- Earliest onset at 1mo.
- Highest incidence rate in second half of 1st year.
- Peaked prevalence at age of 2 for boys, 2.5 for girls.
- Most infants presented with mild AD.
- Severity declined with age.
- Lesions begin at scalp, forehead, ear, neck, elbow, wrist, cheek, ankle, knee, nose, back etc.
- 10 most common regions cheek, knee (flex), chin, chest, upper leg (ext), perioral, upper back, lower back, abdomen, elbow (flex).

Cumulative probability %
Subjects: 356 followed from birth to age 3

Boys
Girls

At Half-Yearly Visits (yr)

<table>
<thead>
<tr>
<th>SCORAD</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
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<tbody>
<tr>
<td>Mild*</td>
<td>43</td>
<td>52</td>
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<td>Moderate</td>
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<td>1</td>
<td>3</td>
<td>3</td>
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</tbody>
</table>

Data are given as mean percentage
SCORAD = Scoring Atopic Dermatitis Index

1. Severity of AD and early food sensitization (wheat, soy) are the strongest associations with prognosis.
2. Children with early AD and early wheezing have impaired lung function at age 7.
Atopic Dermatitis

Environment
- Environmental factors
- Allergens
- Staphylococcus aureus
- Scratching, tissue damage

Skin barrier
- Nonatopic dermatitis
- Sensitization to allergens
- Atopic dermatitis
- Sensitization to self-proteins
- Autoallergic atopic dermatitis
- Impaired epidermal barrier
- Receptors, cytokines, etc.

Host
- Tissue-related genes
- Atopic genes (cytokines, receptors)

Genes

Bieber T, NEJM 2008
Atopic Dermatitis

Bieber T, NEJM 2008
Atopic Dermatitis

Universal criteria for the diagnosis

A. Essential features; must be present and if complete are sufficient for Dx:
   1. Pruritus
   2. Eczematous changes: acute, subacute or chronic
      - Facial and extensor eczema in infants, children
      - Flexural eczema in adults/any age
      - Sparing of groin/ axillary regions
   3. Chronic or relapsing course

B. Important features supporting Dx:
   1. Early age at onset
   2. Atopy (IgE reactivity)
   3. Xerosis

C. Associated features: help but nonspecific
   1. KP, ichthyosis, palmar hyperlinearity
   2. Atypical vascular responses
   3. Perifollicular accentuation, lichenification, prurigo
   4. Ocular/ periorbital changes
   5. Perioral/ periauricular lesions

D. Exclusion: other skin diseases mimicking AD

Leung, Lancet 2003
Simpson & Hanifin, Med Clin N Am 2006
# Atopic Dermatitis

## Differential diagnosis

### Chronic dermatoses:
- Other eczema
- Psoriasis
- Ichtyoses

### Immunological disorders:
- Juvenile dermatomyositis
- Graft versus host disease
- Pemphigus foliaceus
- Dermatitis herpetiformis

### Immunodeficiencies:
- Hyper-IgE syndrome
- Wiskott Aldrich syndrome
- SCID
- DiGeorge syndrome

### Infections and infestations:
- HIV associated dermatitis
- Scabies

### Congenital disorders:
- Netherton’s syndrome
- Familial keratosis pilaris

### Metabolic disorders:
- Zinc deficiency
- Pyridoxine (B6) and niacin
- Multiple carboxylase def
- Phenylketonuria

### Malignant diseases:
- Cutaneous T cell lymphoma
- Letter-Siwe disease

Leung, Lancet 2003
Atopic Dermatitis

Triggers

- Viral infections
- Foods
  - 40% of moderate to severe cases
  - T cells specific to food allergens are cloned from skin lesions
- Staphylococcus aureus
  - Superantigens activate T cells & macrophages, augment synthesis of allergen specific IgE and induce glucocorticoid resistance.
  - Inflammation and scratching related to S. aureus binds to skin.

- Stress
  - Autoallergens
    - IgE against human intracellular proteins
  - Autoallergens released from damaged tissues trigger responses mediated by IgE or T cells.

- Stress
  - Aeroallergens
    - 30-50% + Atopic patch skin test (dust mites, animal dander, molds)
    - Severity associated with degree of IgE sensitization
Atopic Dermatitis

Management

**Skin care:**
- Skin hydration & emollients
- Avoid irritants
- **Elimination of triggers**
- Foods/aeroallergens
- Infections
- **Topical antiinflammatory:**
  - Topical corticosteroids
  - Topical calcineurin inhibitors

**Antihistamines**

**Antibiotics:**
- Topical: Mupirocin, fusidic acid
- Systemic antibiotic

**Systemic corticosteroids**

**Immunomodulators**
- Cyclosporin A
- Azathioprine

**Phototherapy**

**Immunotherapy**

**Education**
Atopic Dermatitis

**Management**

- **Step I**
  - Basic treatment
  - Skin hydration, emollients, avoidance of irritants
  - Identification and addressing of specific trigger factors

- **Step II**
  - Low-mid potency TCS and/or TCI

- **Step III**
  - Mid-high potency TCS and/or TCI

- **Step IV**
  - Systemic therapy (CyA)
  - UV therapy

**Intensity of disease**

- **Dry skin only**
- **Mild to moderate**
- **Moderate to severe**
- **Recalcitrant, Severe**
Topical Glucocorticosteroids

- **Class 1: Superpotent**
  - 0.05% Betamethasone dipropionate gel, ointment
  - 0.05% Clobetasol propionate cream, ointment
- **Class 2: Potent**
  - 0.05% Betamethasone dipropionate cream
  - 0.05% Desoximetasone cream, ointment (Topicort)
  - 0.05% Fluocinonide (Lidex)
  - 0.1% Mometasone ointment
- **Class 3: Upper midstrength**
  - 0.1% Betamethasone valerate
  - 0.005% Fluticasone propionate ointment (Cultivate)
  - 0.1% Mometasone furoate ointment
  - 0.5% Trimacrinolone acetonide
- **Class 4: Midstrength**
  - 0.1% TA ointment/cream
  - 0.025% Fluocinolone acetonide oint
  - 0.05% Desoximetasone cream
- **Class 5: Lower mid-strength**
  - 0.1% TA cream/lotion
  - 0.05% Fluticasone propionate cream
  - 0.025% Fluocinolone acetonide cream
  - 0.1% Betamethasone Valerate cream
- **Class 6: Mild strength**
  - 0.05% Desonide cream
  - 0.01% Fluocinolone (Synalar) cream, lot
  - 0.05% Alclometasone oint
- **Class 7: Least potent**
  - 1, 2.5% hydrocortisone cream, oint
  - Topical with dexamethasone, flumethasone, methylprednisolone and prednisolone
Question 1

A 9 month old infant with on and off itching skin rash since 3 months of age. The rash previously responded to hydrocortisone. Which one is the most likely diagnosis?

A. **Atopic dermatitis**
B. Seborrheic dermatitis
C. Contact dermatitis
D. Scabies
E. Psoriasis
Question 1
2. A 3 yo girl developed swelling lips right after her first bite with fish (tilapia). Father immediately gave a dose of Benadryl and took her to your office. She developed wheezing in the car before arrived your office.

Which one is the most immediate treatment needed?
A. Give second dose of Benadryl
B. Give albuterol nebulizer treatment
C. Give methylprednisolone injection
D. Epinephrine subcutaneous injection
E. Epinephrine intramuscular injection
3. A 4 yo old boy with asthma and allergic rhinitis was tested with positive specific IgE antibodies for pollens and peanut in your office. He had been eating peanut for years without any problems. **Which one is the best recommendation?**

A. Peanut avoidance  
B. Epipen injection with accidental peanut exposure  
C. Take Benadryl before eating peanut  
D. No peanut in his class room  
E. Keep eating peanut
Food Adverse Reactions

Adverse Reaction to Foods

- Nontoxic
  - Immune-mediated
    - Food allergy
      - IgE
      - Non-IgE
      - IgE & Non-IgE
  - Others
    - Metabolic
    - Idiosyncratic
    - Pharmacologic

- Toxic
  - Immune-mediated
    - Food intolerance
  - Others
    - Metabolic
    - Idiosyncratic
    - Pharmacologic
Food Allergy

- True food allergy: Prevalence
  - 6 to 8% of children under 5 years
  - 3 to 4% of adults
Food Allergy

- Culprit foods
  - 8 common foods (90%): cow milk, egg, wheat, soy, peanut, tree nuts, shellfish, fish
  - Others: fruits, sesame seed
# Food Allergy

<table>
<thead>
<tr>
<th>Disorders</th>
<th>IgE-mediated</th>
<th>Mixed mechanism: IgE- and cell-mediated</th>
<th>Non-IgE mediated</th>
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<tbody>
<tr>
<td>Generalized</td>
<td>Anaphylaxis, food-dependent exercise-induced anaphylaxis</td>
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</tr>
<tr>
<td>Cutaneous</td>
<td>Urticaria, angioedema, flushing, acute morbilliform rash, acute contact urticaria</td>
<td>Atopic dermatitis, contact dermatitis</td>
<td>Contact dermatitis, dermatitis herpetiformis</td>
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<tr>
<td>Gastrointestinal</td>
<td>Oral allergy syndrome, gastrointestinal anaphylaxis</td>
<td>Allergic eosinophilic esophagitis, allergic eosinophilic gastroenteritis</td>
<td>Allergic proctocolitis, food protein-induced enterocolitis syndrome, celiac disease, infantile colic</td>
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<tr>
<td>Respiratory</td>
<td>Acute rhinoconjunctivitis, acute bronchospasm</td>
<td>Asthma</td>
<td>Pulmonary hemosiderosis (Heiner's syndrome)</td>
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</tbody>
</table>
## Food Allergy

### IgE-Mediated Food Allergy

#### Clinical Manifestation

<table>
<thead>
<tr>
<th>Organ</th>
<th>Clinical Manifestation</th>
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<tbody>
<tr>
<td>Skin</td>
<td>Pruritus, flushing, urticaria/angioedema, diaphoresis</td>
</tr>
<tr>
<td>Eyes</td>
<td>Conjunctival injection, lacrimation, periorbital edema, pruritus</td>
</tr>
<tr>
<td>Resp</td>
<td>Nose/oropharynx: Sneezing, rhinorrhea, nasal congestion, metallic taste Upper airway: Hoarseness, stridor, sense of choking, laryngeal edema Lower airway: Dyspnea, tachypnea, wheezing, cough, cyanosis</td>
</tr>
<tr>
<td>CVS</td>
<td>Conduction disturbances, tachycardia, bradycardia (if severe), arrhythmias, hypotension, cardiac arrest</td>
</tr>
<tr>
<td>GI</td>
<td>Nausea/vomiting, abdominal cramping, bloating, diarrhea</td>
</tr>
<tr>
<td>Neuro</td>
<td>Sense of impending doom, syncope, dizziness, seizures</td>
</tr>
</tbody>
</table>
Food Allergy

Key History of IgE Mediated Food Allergy

- Symptoms: Involved organs
- Timing: Second to minutes up to 2 hours
- Culprit foods
  - Ask main dish or foods or others: sauces, dressings, breads, beverages, and side dishes eaten before the reactions.
  - Ask potential contaminant or ingredients that are uncommon in the patient's diet.
  - Processed foods also may be mislabeled or contain undeclared allergens.
Food Allergy

Key History of IgE Mediated Food Allergy

- Amount of food eaten
- Hx of avoiding or refusing to eat the suspected food in a young child
- Reproducible or not
- Activity before the reaction: exercise, exertion
- Most recent and most severe reactions
- Treatment required
- Related allergic diseases: AR, asthma, AD
Food Allergy

Diagnostic Tests

• **Prick skin test**
  - Sensitivity > 90% and specificity = 50%
  - Low positive predictive value, High negative predictive value (>95%).
  - The larger the wheal, the greater the likelihood of clinical allergy: cow milk, egg, peanut (> 8mm or 4mm in < 2yrs).
  - Should not perform in the first 4 weeks after anaphylaxis.
  - If anaphylaxis, skin test increases risk of systemic reactions.
Food Allergy

Diagnostic Tests

• Prick-Prick skin test
  – Heat-labile allergens, “Profilin” as an allergens for oral allergy syndrome or pollen-food syndrome
Food Allergy

Diagnostic Tests

• Intradermal skin test
  – Not adding diagnostic value
  – Increased risk of systemic reaction.
Food Allergy

Diagnostic Tests

- Specific IgE antibodies:
  - Unaffected if taking antihistamines or other medications.
  - Useful in patients with severe anaphylaxis in whom skin testing may carry an unacceptable degree of risk.
  - Useful in patients with dermatologic conditions that may preclude skin testing, such as severe atopic dermatitis and dermatographism.
Food Allergy

Diagnostic Tests

• Specific IgE antibodies:
  – Radioallergosorbent test (RAST)
  – ImmunoCap FEIA (Fluorescent enzyme immunoassay)
    • The 95% predictive levels for egg, milk, peanut, tree nuts, and fish.
    • Egg: 7 kUA/L. If < 2 yo, the level is 2 kUA/L.
    • Milk: 15 kUA/L. If < 2 yo, the level is 5 kUA/L.
    • Peanut: 14 kUA/L.
    • Tree nuts: 15 kUA/L.
    • Fish: 20 kUA/L.
Food Allergy

Diagnostic Tests

• Oral food challenge:
  – Gold standard diagnostic tool to confirm diagnosis
  – To determine if an identified allergy persists or has resolved.
Hx: Symptoms & signs, amount of food ingested, timing of reaction to ingestion
Most recent reaction, most severe reaction, treatment
Personal & Fx Hx of atopy: Asthma, AR, AD
PE: V/S, mucocutaneous, respiratory, GI

Consistent with Non-immune mediated

Consistent with IgE-mediated

Prick and/or specific IgE (ImmunoCap)

Hx of anaphylaxis or high PPV test

Strict dietary, food avoidance
Nutritional support
Anaphylaxis treatment plan
Epipen Rx
Medical Alert bracelet

If Hx anaphylaxis, OFC

OFC
Reintroduction of food

Reassessment in a year(s)
With serial testing

Consistent with Non-IgE or Mix
Food Allergy

Anaphylaxis
Food Allergy

Food induced anaphylaxis

When any 1 of the 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of

   - Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula) AND Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
   - Reduced BP or associated symptoms (eg, hypotonia, syncope)

   1 month to 1 yr: Ps <70
   1 to 10 yrs: less than (70 mm Hg + [2 × age])
   11 to 17 yrs: <90 mm Hg.
Food induced anaphylaxis

When any 1 of the 3 criteria are fulfilled:

2. Two or more of the following after exposure to known allergen for that patient (minutes to hours)
   - History of severe allergic reaction
   - Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)
   - Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
   - Reduced BP or associated symptoms (eg, hypotonia, syncope)
   - In suspected food allergy: gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
Food Allergy

Food induced anaphylaxis

When any 1 of the 3 criteria are fulfilled:

3. Hypotension after exposure to known allergen for that patient (minutes to hours)
   - Infants and children:
     - low systolic BP (age-specific) or
     - >30% drop in systolic BP
   - Adults:
     - systolic BP <100 mm Hg or
     - >30% drop from their baseline
Food Allergy

Treatment

• Avoidance
  – Reading labels on commercial food products
  – Ask about ingredients when eating outside the home.
  – Preparation for children at schools or camps
• Being prepared for acute reactions
  – Antihistamine, epinephrine
Food Allergy

Epinephrine

• Who are at risk of food induced Anaphylaxis
  – Prior food allergic reactions involving respiratory and cardiovascular system
  – Generalized urticaria/angioedema
  – Food allergy and asthma or hx of wheezing with any severity
  – Allergy to peanut, nut or seafood
  – Family history with severe food allergic reactions

• How many doses needed
  – Ideally 2 doses

Sicherer SH, JACI 2004
Food Allergy

Route of epinephrine injection

Simons FE, JACI 2001
## Peanut in School: To ban or not to ban

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td>“Loaded gun” argument: reducing chance of exposure to potentially lethal allergen</td>
<td>“No peanut detectors” to enforce ban: very difficult to guarantee “peanut-free school”</td>
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<tr>
<td>Young children cannot bear responsibility, school staff might be inadequate</td>
<td>Might cause undue burden on children without peanut allergy</td>
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<tr>
<td>Food contamination of shared sports equipment and other sources of skin contact</td>
<td>“Slippery slope argument”: ban other foods for other allergies, ban all foods</td>
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<td>Food sharing a common behavior in children</td>
<td>“False sense of security” argument</td>
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<td>School bullying difficult to control</td>
<td>Schools should be preparing students for the “real world”</td>
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<tr>
<td>A community approach to safety</td>
<td>Feelings of divisiveness</td>
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*Young MC, JACI2009*
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<thead>
<tr>
<th>Food</th>
<th>Onset</th>
<th>Resolution</th>
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</thead>
<tbody>
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<td>Cow's milk</td>
<td>6-12 months</td>
<td>76 percent resolve by 5 years</td>
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<tr>
<td>Hen's egg</td>
<td>6-24 months</td>
<td>75 percent resolve by 7 years</td>
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<tr>
<td>Wheat</td>
<td>6-24 months</td>
<td>80 percent resolve by 5 years</td>
</tr>
<tr>
<td>Soybean</td>
<td>6-24 months</td>
<td>67 percent resolve by 2 years</td>
</tr>
<tr>
<td>Peanut</td>
<td>6-24 months</td>
<td>Persistent (20 percent resolve by 5 years)</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>1-7 years</td>
<td>Persistent (9 percent resolve after 5 years)</td>
</tr>
<tr>
<td>Sesame seed</td>
<td>6-36 months</td>
<td>Persistent (20 percent resolve by 7 years)</td>
</tr>
</tbody>
</table>
Indications for Referral to the Allergist

- Diagnosis & assessment of the patient with
  - Severe or persistent disease
  - Multiple food sensitivity
  - Complications
  - Coexisting allergic disease (asthma, atopic dermatitis)
- Test interpretation
- Identification of offending foods
- Performance of food challenges
- Development of targeted elimination diets
- Comprehensive patient education
2. A 3 yo girl developed swelling lips right after her first bite with fish (tilapia). Father immediately gave a dose of Benadryl and took her to your office. She developed wheezing in the car before arrived your office.

Which one is the most immediate treatment needed?
A. Give second dose of Benadryl
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3. A 4 yo old boy with asthma and allergic rhinitis was tested with positive specific IgE antibodies for pollens and peanut in your office. He had been eating peanut for years without any problems.

Which one is the best recommendation?

A. Peanut avoidance
B. Epipen injection with accidental peanut exposure
C. Take Benadryl before eating peanut
D. No peanut in his classroom

E. Keep eating peanut
4. A 7 years-old male complaints of year-round nasal stuffiness with itching and sneezing. 

Which one is the most likely cause of his symptoms?

A. Grasses
B. Trees
C. Weeds
D. House dust mites
E. Molds
5. A 7 years-old male complaints of year-round nasal stuffiness with itching and sneezing. 

Which one is the most effective medication for his symptoms?

A. Second generation of H1 Antihistamines
B. Intranasal antihistamine
C. Ipratropium nasal spray
D. Intranasal corticosteroid
E. Montelukast
Allergic Rhinoconjunctivitis

**Clinical definition**

- Symptomatic disorder of the nose/eyes after allergen exposure by an IgE-mediated inflammation.
- Rhinorrhea, watery eyes, nasal obstruction, itching nose/eyes, sneezing
- Postnasal drip occurs with profuse ant. rhinorrhea or without ant. rhinorrhea; esp. in chronic cases.
- Preschool children may just have nasal obstruction.
- Spontaneously reversible or with treatment
- Non allergic rhinitis may have similar symptoms

Bousquet J, et al. *Allergy* 2008
Table 2: Most Common Chronic Conditions, by Age, Gender and Race

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<th>MALE</th>
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<th>FEMALE</th>
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<tr>
<td></td>
<td>BLACK</td>
<td>WHITE</td>
<td>BLACK</td>
<td>WHITE</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td>Sinusitis</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Hay Fever</td>
<td></td>
<td></td>
<td>Orthopedic</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>impairments</td>
<td></td>
</tr>
<tr>
<td>Orthopedic impairments</td>
<td></td>
<td></td>
<td>Hay Fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hearing impairments</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>18-44</strong></td>
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</tr>
</tbody>
</table>

Data from 3 national surveys of the community-dwelling population living within the US (1994)

National Academy on an Aging Society, 2000
Allergic Rhinoconjunctivitis

Classification
• Seasonal allergic rhinoconjunctivitis (20%)
• Perennial allergic rhinoconjunctivitis (40%)
• Mixed-Perennial allergic rhinoconjunctivitis with seasonal exacerbations (40%)
Allergic Rhinoconjunctivitis
### Causes of Rhinitis

- **Allergic rhinitis**
- **Infectious rhinitis** (acute, chronic)
- **Perennial nonallergic rhinitis** (Vasomotor rhinitis)
- **Nonallergic rhinitis**
  - Structural/mechanical factors
  - Hypertrophic turbinates
  - Adenoidal hypertrophy
  - Foreign bodies
  - Nasal tumors
  - Choanal atresia
  - Emotional factors
  - Environmental factors
    - Odors, Temperature
    - Weather/barometric pressure

- **Hormonally induced**
  - Hypothyroid, pregnancy
  - Contraceptive pills, menses

- **Drug induced**
  - Antihypertensive therapy
  - Rhinitis medicamentosa
  - NSAID, Contraceptive pills

- **Reflex induced**
  - Gustatory rhinitis,
  - Chemical/irritant induced
  - Nasal cycle

- **Inflammatory/immunologic**
  - Wegener granulomatosis
  - Sarcoidosis
  - Mildline granuloma
  - SLE, Sjogren syndrome

---

Allergic Rhinoconjunctivitis

Bieber T, NEJM 2008
Allergic Rhinoconjunctivitis

Early phase: Mediator (minutes)
- Nerve: Sneezing & itching
- Gland: Rhinorrhea
- Blood Vessels: Congestion

“Sneezer”

Late phase: Cellular (hours -> days)
- Priming effect
- Hyperreactivity
- Acute & Chronic inflammation
- Tissue remodeling

“Blocker”

Mast cell

Ag
Histamine

MC → Histamine → CH₂CH₂NH₂ → H1-Receptor Degradation

Nociceptive Nerves (Axon Response?) → Itch

CNS

Systemic Reflexes
Sneeze
Allergic Salute
Parasympathetic Reflexes
Glandular Exocytosis

Endothelium (Vascular Permeability)

Mucus Secretion

Adapted from Baraniuk JN. Pathogenesis of allergic rhinitis. JACI 1997; 99:2
Allergic Rhinoconjunctivitis

Allergens

Perennial
- Dust mites
- Animals (Cat/dog)
- Cockroaches
- Molds
- Occupational or Hobby-Related

Seasonal
- Trees (Spring)
- Grasses (Summer)
- Weeds (Fall)

Nonspecific
- Cigarette Smoke
- Odors, Fumes
- Change in Temperature
Allergic Rhinoconjunctivitis

Impact in children

- Quality of life
  - Cough
  - Fatigue, malaise
  - Emotional Limitation
  - Activity Limitation
  - Sleep disturbance, sleep apnea?

- Learning problems

- School/ work performance impairment

- Contributing to other illnesses

- Healthcare costs

Allergic Rhinoconjunctivitis

Meltzer et al. JACI 2009
Allergic Rhinoconjunctivitis

- **Been happy**: 28% (Allergies) vs. 32% (No allergies)
- **Calm and peaceful**: 18% (Allergies) vs. 29% (No allergies)
- **Lots of energy**: 32% (Allergies) vs. 50% (No allergies)
- **Full of life**: 32% (Allergies) vs. 51% (No allergies)

*Meltzer et al. JACI 2009*
Allergic Rhinoconjunctivitis

OM with Effusion
Nasal Polyposis
URI
Atopic dermatitis
Food allergy
Asthma
Sinusitis

Adapted from Meltzer EO, et al. *Ann Allergy Asthma Immunol* 1999; 83: 455-463
Prick Skin Test

Ag

Mast cell
Intradermal Skin Test

Ag → Mast cell

Mast cell release histamine and other mediators.
<table>
<thead>
<tr>
<th></th>
<th>Prick test</th>
<th>Intradermal test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of specific IgE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>+++</td>
<td>+++++</td>
</tr>
<tr>
<td>Specificity</td>
<td>+++++</td>
<td>+++</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>+++</td>
<td>+++++</td>
</tr>
<tr>
<td>False positive</td>
<td>Rare</td>
<td>Possible</td>
</tr>
<tr>
<td>False negative</td>
<td>Possible</td>
<td>Rare</td>
</tr>
<tr>
<td>Simplicity</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Speed</td>
<td>+++++</td>
<td>++</td>
</tr>
<tr>
<td>Easiness of Interpretation</td>
<td>+++++</td>
<td>++</td>
</tr>
<tr>
<td>Safety</td>
<td>+++++</td>
<td>++</td>
</tr>
<tr>
<td>Discomfort</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Testing of infants</td>
<td>Yes</td>
<td>Difficult</td>
</tr>
<tr>
<td>Clinical use</td>
<td>All allergic disease</td>
<td>Insect, drug, some aeroallergens</td>
</tr>
</tbody>
</table>

Modified from Middleton's Allergy 7th ed
Allergic Rhinocconjunctivitis

Stepwise Management

Mild
- Antihistamine (non sedating) +/- Decongestants
- Topical corticosteroids
- Allergen Immunotherapy
- Allergen avoidance

Moderate
- Combined therapy, Oral steroid?
- Antihistamine (non sedating) +/- Decongestants
- Topical corticosteroids
- Allergen Immunotherapy
- Allergen avoidance

Severe
- Combined therapy, Oral steroid?
These are Your Rhinitis and Allergic Conjunctivitis Medications

<table>
<thead>
<tr>
<th>Antihistamines</th>
<th>Nasal Corticosteroids</th>
<th>Oral Decongestants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegra (fexofenadine)</td>
<td>D (tab)</td>
<td>Syrup</td>
</tr>
<tr>
<td>Claritin (loratadine)</td>
<td>D (tab)</td>
<td>Syrup</td>
</tr>
<tr>
<td>Clotrim (desloratadine)</td>
<td>D (tab)</td>
<td>Syrup</td>
</tr>
<tr>
<td>Zyrtec (cetirizine)</td>
<td>D (tab)</td>
<td>Syrup</td>
</tr>
<tr>
<td>Benadryl</td>
<td>D (tab)</td>
<td>Syrup</td>
</tr>
</tbody>
</table>

Leukotriene Modifiers

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Singular</td>
<td>Syrup</td>
<td></td>
</tr>
</tbody>
</table>

Mast Cell Inhibitors

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasonex (cromolyn)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anti-inflammatory

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrovent Nasal Spray</td>
<td>1%</td>
<td>0.06%</td>
</tr>
</tbody>
</table>

Inhaler/Lubricant

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Saline/moisturizer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What to do for Increased Nasal Symptoms

- You have a cold
- It is your allergy season
- You are exposed to your triggers
- First take your step 1 or step 2 medicine

<table>
<thead>
<tr>
<th>Green Zone</th>
<th>Yellow Zone</th>
<th>Red Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Episode</td>
<td>Moderate Episode</td>
<td>Severe Episode</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response to medicine</td>
<td>Poor response to medicine</td>
<td>Moderate to severe Nasal Symptoms</td>
</tr>
<tr>
<td>No Nasal Symptoms</td>
<td>Step up 1 level</td>
<td>Step up 3 levels</td>
</tr>
<tr>
<td>Step up 2 levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long-Term Management of Nasal Symptoms

<table>
<thead>
<tr>
<th>Controlled</th>
<th>Fair Control</th>
<th>Not Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>No interference with activities</td>
<td>Mid interference with activities</td>
<td>Severe interference with activities</td>
</tr>
<tr>
<td>2-3 days per week sneezing, itching, congestion, eye symptoms</td>
<td>Increase treatment by one step</td>
<td>Increase treatment by 2 steps</td>
</tr>
<tr>
<td>Stay at the same step or consider stepping down</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dust Mite Control

• **Bed room:**
  – Dust mite proof covers for mattress, pillows
  – Wash sheets, pillowcases, and blankets in warm water with detergent or dry in an electric dryer on the hot setting weekly
  – Remove comforter, clutter, soft toys, books and upholstered furniture
  – Use washable, vinyl, or roll-type window covers
  – If possible, remove carpet and use washable area rugs

• **Rest of the house:**
  – Reduce upholstered furniture, particularly old sofas.
  – Replace carpets with polished flooring where possible
  – Vacuum weekly using a cleaner with a HEPA filtration system.
  – Window coverings should be washable, vinyl, or roll type.
  – Use humidifier to control humidity to <50% relative humidity.

• **No role:** Acaricides, denaturants, airfilters
• Removing animal from the house
• Controlling allergen with an animal in the house
  – Reduce reservoirs: remove carpets, reduce upholstered furniture to a minimum, replace drapes with blinds, or/and vacuum clean weekly using a vacuum with good filtration (Double thickness bags and/or HEPA filtration).
  – Room air filters: HEPA or electrostatic.
  – Washing dogs x 2/week
  – Washing cats does not reduce allergen levels
Pollen Avoidance

- Keep window and door shut.
- Use air conditioning in the home.
- Avoid early morning outdoor exposure.
- Shower and change clothes after outdoor activities.
- Avoid using towels and bedding dried outside.
- Avoid having indoor plants.
- Keep animal outside, since pollens can be transported on animal furs.
Saline drops/spray
- Remove mucus, reduce inflammation
- 2-6 spray as needed

Intranasal Cromolyn Sodium
- Mild to moderate
- Prophylactic agent before allergen exposure, onset of season
- Need 1 spray qid
## Oral and Intranasal Antihistamine

<table>
<thead>
<tr>
<th>Second generation</th>
<th>Trade name</th>
<th>Age limit</th>
<th>Pediatric dose</th>
<th>Adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>Zyrtec</td>
<td>6 mo</td>
<td>2.5mg (6m-5yr) qd 5-10mg (6y-11yr) qd</td>
<td>5-10mg qd</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>Xyzal</td>
<td>6 mo</td>
<td>1.25mg qd (6m-5yr) 2.5mg qd (6y-11yr)</td>
<td>5mg qid</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Claritin</td>
<td>2yr</td>
<td>5mg qd (2y-5yr) 2.5mg qd (6y-11yr)</td>
<td>10mg qd</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>Clarinex</td>
<td>6 mo</td>
<td>2ml (1mg) qd(6m-11m) 2.5ml (1.25mg) qd (12m-5yr) 5ml (2.5mg) qd (6-11yr)</td>
<td>5mg qd</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Allergra</td>
<td>6 mo</td>
<td>2.5 ml (15mg) bid (6m-2yr) 30mg bid (2-11yr)</td>
<td>180mg bid</td>
</tr>
<tr>
<td>Azelastine</td>
<td>Astelin, Astepro</td>
<td>5yr</td>
<td>1-2sp/nose bid</td>
<td>2 sp/nose bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otoptadine</td>
<td>Patanase</td>
<td>12 yr</td>
<td>2sp/nase bid</td>
<td>2 sp/ nose bid</td>
</tr>
</tbody>
</table>
Intranasal Antihistamine

Azelastine (Astelin® 137mcg or Astepro ® 205.5mcg)

- Bioavailability of about 40%.
  - Seasonal (Astelin & Astepro) perennial AR (Astepro)
  - Vasomotor rhinitis (2 sprays BID)
  - Rapid onset of action (15mins-45mins)
  - Prolonged duration (12 to 24 hours)

- Side effects:
  - Bitter taste (75%)
  - Somnolence (11.5% vs 5.4% placebo)
  - Headache
  - Nasal burn
  - Rhinitis

Lieberman P, Management of allergic rhinitis with a combination antihistamine/anti-inflammatory agent JACI 1999
## Antihistamine

<table>
<thead>
<tr>
<th>Diseases/Conditions</th>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Allergic rhinoconjunctivitis</td>
<td>1A</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1A</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1B</td>
</tr>
<tr>
<td>Asthma</td>
<td>1C</td>
</tr>
<tr>
<td>URI infection (Colds)</td>
<td>3D</td>
</tr>
<tr>
<td>Otitis media</td>
<td>3D</td>
</tr>
<tr>
<td>Others (mosquito bite, eosinophilic cellulitis, etc)</td>
<td>1B</td>
</tr>
</tbody>
</table>

**Level 1** = Randomized controlled, clinical trial  
**Level 2** = Case-control cohort study  
**Level 3** = Consensus of expert group  

A = good evidence for use  
B = Some evidence for use  
C = evidence neither for nor against use  
D = some evidence against use  
E = Strong evidence against use
Effects of Intranasal Corticosteroids

Adapted from Barnes PJ. Current issues for the establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma. Day J Allergy Clin Immunol 1998 Mar;101: S427-S433
<table>
<thead>
<tr>
<th>Drug</th>
<th>Age limit (Y)</th>
<th>Usual child dose</th>
<th>Alcohol</th>
<th>BKC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedesonide (Rhinocort)</td>
<td>6</td>
<td>1-2 sp/nose qd</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Beclomethasone (Beconase)</td>
<td>6</td>
<td>1-2 sp/nose bid</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluticasone propionate (Flonase)</td>
<td>4</td>
<td>1-2 sp/nose qd</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flunisolide (Nasarel)</td>
<td>6</td>
<td>2 sp/nose bid</td>
<td>Propylene glycol</td>
<td>Yes</td>
</tr>
<tr>
<td>Momentasone (Nasonex)</td>
<td>2</td>
<td>1 sp/nose qd</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Triamcinolone (Nasocort)</td>
<td>6</td>
<td>1-2 sp/nose qd</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Ciclesonide (Omnaris)</td>
<td>12</td>
<td>NA</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Fluticasone furoate (Veramyst)</td>
<td>2</td>
<td>1 sp/nose qd</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Intranasal Corticosteroid

Technique of Nasal spray use

Efficacy of Intranasal corticosteroids

Nasal blockage
Nasal discharge
Sneezing
Nasal itch
Postnasal drip
Total nasal symptoms
Quality of life

Intranasal corticosteroids produced significantly greater relief than oral antihistamines.

Anti-Leukotriene Agents

Nayak and Langdon, Drugs 2007
Ipratropium Bromide (0.06%, 0.03% Atrovent)

- **Mechanism of action:**
  - Blockage of muscarinic receptors of seromucinous glands
  - Effective only in controlling watery nasal discharge
    - Seasonal, perennial AR
    - Non allergic rhinitis
    - Common cold
  - Need 3-4 time of administration
    - Seasonal, perennial AR
    - Common cold

- **Local side effects:** dryness, irritation, burning

Herbal Medicines

Butterbur leaf extract Ze 339
(CO2 extract from the leaves of Petasites hybridus L., 8 mg petasines/tab)

Kaufeler R et al. Adv Ther 2006

An open postmarketing surveillance study: 2 tabs/day for 2wks

- 580 subjects treated & evaluated on a visual analogue scale for rhinorrhea, sneezing, nasal congestion, itchy eyes/nose, red eyes, and skin irritation.
- 90% improvement. Differences observed before & after therapy were significant and clinically relevant for all symptoms.
- The improvement was inversely related to symptom severity.
- 80% Efficacy, 92% tolerability, and 80% improvement in quality of life.
- 44% of patients given an antiallergic comedication and Ze 339 did not result in a better effect than was attained with Ze 339 monotherapy.
- 3.8% adverse events (GI complaints predominantly)
Allergen-Specific Immunotherapy

- ↓ Allergen-specific IgE
- ↓ Seasonal increases in IgE
- ↑ Blocking antibodies: IgG1, IgG4 and IgA
- ↑ IL-10

- ↓ Allergen-specific proliferation
- ↓ Tissue numbers in late-phase reactions
- ↓ T_{h2}-cell cytokines in tissues
- ↑ T_{h1}-cell cytokines in tissues
- ↑ T_{reg} cells, IL-10 and TGFβ

- ↑ IL-10

- ↓ Tissue numbers
- ↓ Mediator release
Consultation with an allergist/immunologist

1. Prolonged manifestation of rhinitis
2. Complications of rhinitis, such as OM, sinusitis, and/or nasal polyposis
3. Comorbid condition such as asthma
4. Required systemic corticosteroid for the treatment of rhinitis
5. Symptoms or medication side effects interfere with his/her ability to function such as causing sleep disturbance or impairing school/work performance.
6. Symptoms significantly decrease QOL such as a decrease in comfort and well being, sleep disturbance, anosmia, ageusia
Consultation with an allergist/immunologist

7. Medications for rhinitis is ineffective or produces adverse events
8. Rhinitis medicamentosa
9. Allergic/environmental triggers symptoms need further identification and clarification.
10. Need for more complete education.
11. Requiring multiple and/or costly medications over a prolong period.
12. Allergy immunotherapy is a treatment consideration.
6. A 2 year-old boy presents with recurrent sinus infections, low IgG, normal CBC, normal IgM, IgA, IgE, normal tetanus, HIB, pneumococcal titers and normal lymphocyte subpopulations (CD3, CD4, CD19, CD56).

Which one is the best recommendation?

A. Antibiotic prophylaxis
B. IVIG replacement therapy
C. Bone marrow transplantation
D. Gene therapy
E. Good hygiene, observation, recheck IgG in a couple years
Primary Immunodeficiencies (PID)

Articles published

Orange JS. Immunol Allergy Clin N Am 2008
Primary Immunodeficiencies

- 2.5% Complement deficiencies
- 2.7% Genetic disorders of immune regulation
- 8.4% Combined T and B cell immunodeficiencies
- 11.2% Phagocytic defects
- 18.3% Other well-defined immunodeficiencies
- 0.4% Autoinflammatory disorders
- 0.4% Defects in innate immunity: receptors & B signaling components
- 56% Antibody deficiencies

Rezaei N et al. Primary Immunodeficiency Diseases 2008
Primary Immunodeficiencies

Symptomatic recognition → Diagnosis → Clinical interventions

Natural history of disease

Asymptomatic | Symptomatic

Birth | Early clinical disease | Late sequelae | Disability | Death

Modified from MMWR 2004
Immune System
Innate Immunity

Magnitude of responses

Inflammatory immune response

Granulocytes, Macrophages

Dendritic cells (DC)
Natural Killer cells (NK)

TLRs
NLRs
RLRs
Cytokines
Interferons
IgM

Antigen-presenting
NK killing

Antigen-specific
1. Antibodies (IgG, A, E)
2. Cellular immune response
   (CTL, Th, Treg)

TLRs
NLRs
RLRs
Cytokines
Interferons
IgM

Innate Immunity

Adaptive immunity

T cells, B cells

The major effector cells functions

Minutes
Hours
Days
Months
Years

Rich. Clinical Immunology 2007
Features of Immune System Failure

Self VS Non-self Recognition

- Infection
- Allergy
- Autoimmunity
- Autoinflammatory disorders
- Malignancy

Adaptive Immunity

Stiehm et al. Immunology disorders in Infants & Children 2004
Absolute lymphocyte count < 2,800 in infants needs further work up

Pediatr Infect Dis J 2005;24:595-600
# Lymphocyte Subsets

<table>
<thead>
<tr>
<th>Marker name</th>
<th>Cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>T cell</td>
</tr>
<tr>
<td>CD4</td>
<td>T cell subset</td>
</tr>
<tr>
<td>CD8</td>
<td>T cell subset</td>
</tr>
<tr>
<td>CD19, CD20</td>
<td>B cell</td>
</tr>
<tr>
<td>CD16</td>
<td>NK cell (may not present in some NKs)</td>
</tr>
<tr>
<td>CD56</td>
<td>NK cell (majority)</td>
</tr>
</tbody>
</table>
# Lymphocyte Functions

<table>
<thead>
<tr>
<th>Cell</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cells</td>
<td>• Immunoglobulins (IgG, A, M, E)</td>
</tr>
<tr>
<td></td>
<td>• Specific antibodies (HIB, Pneumo, Tetanus)</td>
</tr>
<tr>
<td>T cells</td>
<td>• Delayed type hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>• Lymphocyte mitogen stimulation</td>
</tr>
<tr>
<td></td>
<td>(PHA, ConA, Pookweed, PMI/Io)</td>
</tr>
<tr>
<td></td>
<td>• Lymphocyte antigen stimulation</td>
</tr>
<tr>
<td></td>
<td>(Candida, Tetanus, Diptheria)</td>
</tr>
<tr>
<td>NK cells</td>
<td>• NK cell function</td>
</tr>
</tbody>
</table>
Non-Immunologic Causes

Recurrent infections

- Abnormal mucous membranes and integuments:
  - Burns, severe eczema, bullous diseases, ectodermal dysplasia, percutaneous catheters.

- Obstruction of hollow viscus:
  - Allergic rhinitis, adenoid hypertropy with Eustachian tube dysfunction, asthma, cystic fibrosis, inhaled foreign body, posterior urethral valves, ureteropelvic junction obstruction.

- Foreign body:
  - Ventriculoperitoneal shunt, prosthetic cardiac valves, orthopedic devices, catheters.

- Vascular abnormalities:
  - Large left to right intracardiac shunt, diabetes mellitus.
Non-Immunologic Causes

Recurrent infections

• Congenital:
  – Cysts and sinus tracts, tracheoesophageal fistula, abnormal ciliary function.

• Neurologic:
  – Incoordinate swallowing, recurrent aspiration, poor respiratory effort.

• Metabolic disorders:
  – Galactosemia, certain amino acid and organic acid disorders.

• Unusual microbiologic factors:
  – Antibiotic overgrowth, resistant organism, continuous reinfection.
Secondary Immunodeficiency

- Premature and Newborn
- Hereditary & Metabolic Diseases:
  - Chromosomal abnormalities (Down syndrome, etc)
  - Uremia, DM, NS, myotonic dystrophy
  - Malnutrition, vitamin & mineral deficiency
  - Protein-losing enteropathies,
- Immunosuppressive agents & Radiation
- Infectious diseases:
  - Congenital rubella, viral examthem (measles, varicella, etc)
  - HIV, CMV, EBV
  - Bacterial infections, mycobacterial, fungal, parasite.
Secondary Immunodeficiency

• Infiltrative & Hematologic diseases
  – Histiocytosis, lymphoma, leukemia, myeloma
  – Agranulocytosis, aplastic anemia, cyclic neutropenia
  – Transplant recipients

• Surgery & Trauma
  – Burns, head injury, hypothermia
  – Splenectomy, anesthesia

• Miscellaneous
  – SLE, alcoholic hepatitis, chronic active hepatitis, etc.
  – Aging
Clinical Features of PID

Abnormal labs
- Low Ig, ab titers
- Lymphopenia, Neutropenia
- Low Complements

Problems
- Sinopulmonary infections
- Opportunistic infections
  - Recurrent abscess
  - Severe eczema
- Delayed cord separation
  - FTT
- No lymphoid organs
- Autoimmune diseases
- Specific bacteria/virus

Exams
- G & D
- Facies
- LN
- Lung
- Heart
- Abd
- Ext
- Skin

Age at onset
- After 6 mo
- First 5yo
- Later

Ad lt
- Problems
- Sinopulmonary infections
- Opportunistic infections
  - Recurrent abscess
  - Severe eczema
  - Delayed cord separation
    - FTT
  - No lymphoid organs
  - Autoimmune diseases
  - Specific bacteria/virus

Family (XL AD)
- Heart
- Abd
- Ext
- Skin

Underlying diseases
- Autoimmune diseases
- Specific bacteria/virus
# Clinical Features of PID

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal period</td>
<td>• Omenn syndrome</td>
</tr>
<tr>
<td></td>
<td>• Severe congenital neutropenia</td>
</tr>
<tr>
<td></td>
<td>• DiGeorge syndrome</td>
</tr>
<tr>
<td></td>
<td>• LAD</td>
</tr>
<tr>
<td></td>
<td>• Reticular dysgenesis</td>
</tr>
<tr>
<td>First 6 months</td>
<td>• SCID</td>
</tr>
<tr>
<td></td>
<td>• Other T cell deficiency</td>
</tr>
<tr>
<td></td>
<td>• CD40 ligand deficiency</td>
</tr>
</tbody>
</table>
Omenn’s Syndrome

Generalized scaly exudative erythroderma, enlarged lymphoid tissues
Protracted diarrhea, FTT, eosinophilia, hypogammaglobulinemia
Genetic defects: RAG1, ARG2, Artemis, ADA deficiency, IL7Ra

Abundant lymphocytic infiltrate in superficial dermis with keratinocytes damage and eosinophil infiltrate
Leukocyte Adhesion Defect (LAD)
Leukocyte Adhesion Defect (LAD)

Hallmarks: Gingivitis, severe periodontitis, failure to form pus, limited inability to demarcate the fibrotic skin debris, and limited inflammation.
### When an umbilical cord separates

#### Cord care regimen and days to umbilical cord separation

<table>
<thead>
<tr>
<th>Cord Care Regimen</th>
<th>Author</th>
<th>Mean Time to Separate (d)</th>
<th>Standard Deviation</th>
<th>Range (d)</th>
<th>Number of Infants Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry care</td>
<td>Dore et al 1998 (15)</td>
<td>8.16</td>
<td>±3.1</td>
<td>1 to 24</td>
<td>907</td>
</tr>
<tr>
<td>Dry care</td>
<td>Mugford et al 1986 (16)</td>
<td>7.27</td>
<td>±2.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Care</td>
<td>Oudesluys-Murphy et al 1990 (26)</td>
<td>7.4</td>
<td>±3.3 days</td>
<td>1 to 29</td>
<td>911</td>
</tr>
<tr>
<td>Dry care</td>
<td>Pezzati et al 2002 (20)</td>
<td>7.5</td>
<td>±3.1 days</td>
<td></td>
<td>177</td>
</tr>
<tr>
<td>Triple dye</td>
<td>Pezzati et al 2002 (20)</td>
<td>11.6</td>
<td>±6.6 days</td>
<td></td>
<td>195</td>
</tr>
<tr>
<td>70% alcohol</td>
<td>Dore et al 1998 (15)</td>
<td>9.8</td>
<td>±4.6</td>
<td>2 to 49</td>
<td>900</td>
</tr>
<tr>
<td>70% alcohol</td>
<td>Golombek et al 2002 (27)</td>
<td>10</td>
<td>±2.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% alcohol</td>
<td>Mugford et al 1986 (16)</td>
<td>7.14</td>
<td>±7.5 days</td>
<td></td>
<td>178</td>
</tr>
<tr>
<td>70% alcohol</td>
<td>Pezzati et al 2002 (20)</td>
<td>16.9</td>
<td>±7.5 days</td>
<td></td>
<td>178</td>
</tr>
<tr>
<td>70% alcohol</td>
<td>Rais-Bahrami et al 1993 (28)</td>
<td>10.9</td>
<td>±2.3 days</td>
<td>3 to 43</td>
<td>293</td>
</tr>
<tr>
<td>Salicylic acid powder</td>
<td>Pezzati et al 2002 (20)</td>
<td>5.6</td>
<td>±2.3 days</td>
<td></td>
<td>167</td>
</tr>
</tbody>
</table>

JoDee M, et al. NeoReviews 2004
SCID

Clinical Features of PID

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 6 months- 5 years</td>
<td>• Hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>• Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td></td>
<td>• Phagocytic defects</td>
</tr>
<tr>
<td></td>
<td>• DiGeorge syndrome</td>
</tr>
<tr>
<td></td>
<td>• Chronic mucocutaneous candidiasis</td>
</tr>
<tr>
<td>After 5 years</td>
<td>• Late presentation of the above</td>
</tr>
<tr>
<td></td>
<td>• AT, other DNA repair disorder</td>
</tr>
<tr>
<td></td>
<td>• CVID</td>
</tr>
<tr>
<td></td>
<td>• Specific antibody deficiency</td>
</tr>
<tr>
<td></td>
<td>• Complement disorder</td>
</tr>
</tbody>
</table>
Wiskott-Aldrich syndrome (WAS)

Clinical Features
- Petechiae due to thrombocytopenia
- Eczema
- Pneumonia and other infections
- B-cell lymphoma and other cancers

WASP Structure
- WASP homology: 1-137
- BR: 210
- GTPase: 230
- Proline-rich region: 310-312
- V: 417-423
- C: 502

Chronic Granulomatous Disease (CGD)

- Painful inflammation of the nares
- Severe gingivitis
- Aspergillus pneumonia
- Large granuloma in the neck
- Wound dehiscence & impaired wound healing at the surgical incision sites
- Esophageal stricture caused by granuloma

### Clinical Features of PID

<table>
<thead>
<tr>
<th>Organism</th>
<th>Candidate immune defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcus, HIB</td>
<td>• B cell/ Antibody&lt;br&gt;• Complement</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>• Neutrophil</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>• Complement (Late C5-C9)</td>
</tr>
<tr>
<td>Gram negative bacteria</td>
<td>• Neutrophil</td>
</tr>
<tr>
<td>Salmonella</td>
<td>• Cell–mediated&lt;br&gt;• Type 1 cytokine defects</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>• B cell/antibody&lt;br&gt;• Cell mediated</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>• Cell mediated</td>
</tr>
</tbody>
</table>
## Clinical Features of PID

<table>
<thead>
<tr>
<th>Organism</th>
<th>Candidate immune defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma</td>
<td>• B cell/ Antibody</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>• Cell mediated</td>
</tr>
<tr>
<td></td>
<td>• Neutrophil</td>
</tr>
<tr>
<td></td>
<td>• Monocyte</td>
</tr>
<tr>
<td>Aspergillus spp</td>
<td>• Neutrophil</td>
</tr>
<tr>
<td>Herpes viruses (eg CMV)</td>
<td>• Cell-mediated</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>• Antibody</td>
</tr>
<tr>
<td></td>
<td>• Cell–mediated</td>
</tr>
<tr>
<td>Other viruses (eg measles)</td>
<td>• Cell mediated</td>
</tr>
</tbody>
</table>

Adapted from Slatter MA. *Clin Exp Immunol* 2008
Clinical Features of PID

<table>
<thead>
<tr>
<th>Organism</th>
<th>Candidate immune defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>• Cell-mediated</td>
</tr>
<tr>
<td></td>
<td>• Type 1 cytokine defects</td>
</tr>
<tr>
<td></td>
<td>IFN-gR1</td>
</tr>
<tr>
<td></td>
<td>IFN-gR2</td>
</tr>
<tr>
<td></td>
<td>STAT1,</td>
</tr>
<tr>
<td></td>
<td>IL-12RB1</td>
</tr>
<tr>
<td></td>
<td>IL-12B</td>
</tr>
<tr>
<td>Mycobacteria (typical &amp; atypical)</td>
<td>• Type 1 cytokine defects</td>
</tr>
<tr>
<td></td>
<td>• NFkB signalling pathway defects (NEMO)</td>
</tr>
</tbody>
</table>

Adapted from Slatter MA. Clin Exp Immunol 2008
<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract infections</td>
<td>• SCID</td>
</tr>
<tr>
<td>Persistent sinopulmonary infections</td>
<td>• Hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>• Specific antibody def</td>
</tr>
<tr>
<td></td>
<td>• Complement deficiency</td>
</tr>
<tr>
<td></td>
<td>• Cyclic neutropenia</td>
</tr>
<tr>
<td></td>
<td>• NEMO</td>
</tr>
<tr>
<td></td>
<td>• IRAK4 deficiency</td>
</tr>
<tr>
<td>Recurrent skin infection, periodontitis</td>
<td>• CGD</td>
</tr>
<tr>
<td>gingivostomatitis</td>
<td>• HIE</td>
</tr>
<tr>
<td></td>
<td>• LAD</td>
</tr>
<tr>
<td></td>
<td>• XLA</td>
</tr>
<tr>
<td></td>
<td>• Neutropenia</td>
</tr>
</tbody>
</table>
# Clinical Features of PID

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Immunodeficiency</th>
</tr>
</thead>
</table>
| Eczema                        | • HIE  
  • WAS  
  • Omenn’s syndrome  
  • Netherton syndrome  
  • CGD  
  • IPEX  
  • Hypogammaglobulinemia (CVID, HIM, IGAD, XLA) |
| Recurrent mucosal candidiasis | • SCID  
  • Chronic mucocutaneous candidiasis  
  • HIE |
<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract infections</td>
<td>• SCID</td>
</tr>
<tr>
<td>Persistent sinopulmonary infections</td>
<td>• Hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>• Specific antibody def</td>
</tr>
<tr>
<td></td>
<td>• Complement deficiency</td>
</tr>
<tr>
<td></td>
<td>• Cyclic neutropenia</td>
</tr>
<tr>
<td></td>
<td>• NEMO</td>
</tr>
<tr>
<td></td>
<td>• IRAK4 deficiency</td>
</tr>
<tr>
<td>Recurrent skin infection, periodontitis,</td>
<td>• CGD</td>
</tr>
<tr>
<td>gingivostomatitis</td>
<td>• HIE</td>
</tr>
<tr>
<td></td>
<td>• LAD</td>
</tr>
<tr>
<td></td>
<td>• XLA</td>
</tr>
<tr>
<td></td>
<td>• Neutropenia</td>
</tr>
</tbody>
</table>
Clinical Features of PID

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>• XLA</td>
</tr>
<tr>
<td></td>
<td>• CVID</td>
</tr>
<tr>
<td></td>
<td>• HIM</td>
</tr>
<tr>
<td></td>
<td>• IGAD</td>
</tr>
<tr>
<td></td>
<td>• WHIM</td>
</tr>
<tr>
<td></td>
<td>• Cartilage-hair hypoplasia</td>
</tr>
<tr>
<td></td>
<td>• Reticular dysgenesis</td>
</tr>
<tr>
<td></td>
<td>• Dubowitz syndrome</td>
</tr>
<tr>
<td></td>
<td>• Griscelli syndrome</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>• WAS</td>
</tr>
<tr>
<td></td>
<td>• DiGeorge syndrome</td>
</tr>
<tr>
<td></td>
<td>• CVID</td>
</tr>
<tr>
<td></td>
<td>• CGD</td>
</tr>
</tbody>
</table>
## Clinical Features of PID

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telangiectasia</td>
<td>• Ataxia telangiectasia</td>
</tr>
<tr>
<td>Absence or scanty lymphoid tissues</td>
<td>• XLA</td>
</tr>
<tr>
<td></td>
<td>• SCID</td>
</tr>
<tr>
<td></td>
<td>• Complete DiGeorge anomaly</td>
</tr>
<tr>
<td>Delayed cord separation</td>
<td>• LAD</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>• AT</td>
</tr>
<tr>
<td></td>
<td>• WAS</td>
</tr>
<tr>
<td></td>
<td>• XLP</td>
</tr>
<tr>
<td></td>
<td>• CVID</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>• HIM (CD40 ligand def)</td>
</tr>
</tbody>
</table>
Warning Signs

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.

2 or more of the warning sings

Presented as a public service by:
Jeffrey Modell Foundation
History of respiratory infections in the first 12 yr among children from a birth cohort

1314 German children born in 1990 tracked until age 12 yr (760 children)

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal number of respiratory tract infection episodes per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (0-2 Yr)</td>
<td>11</td>
</tr>
<tr>
<td>Pre-school age (3-5 Yr)</td>
<td>8</td>
</tr>
<tr>
<td>School age (6-12 Yr)</td>
<td>4</td>
</tr>
</tbody>
</table>

Warning Signs

6. Recurrent, deep skin or organ abscesses.

7. Persistent thrush in mouth or elsewhere on skin, after age 1.

8. Need for intravenous antibiotics to clear infections.

9. Two or more deep-seated infections.

10. A family history of Primary Immunodeficiency.

2 or more of the warning sings

Presented as a public service by: Jeffrey Modell Foundation
Underlying causes of recurrent pneumonia in children

238 children (2.5 mo-15.6yr)
220 (92%) with underlying causes, 18 (8%) with unknown cause

<table>
<thead>
<tr>
<th>Underlying illness</th>
<th>Mean age</th>
<th>Dx prior to pneumonia</th>
<th>Dx after 1st pneumonia</th>
<th>Dx after recur pneumonia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration syndrome</td>
<td>6.3yr</td>
<td>109</td>
<td>1</td>
<td>4</td>
<td>114</td>
</tr>
<tr>
<td>Immune disorder</td>
<td>3.8yr</td>
<td>26</td>
<td>7</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Cong heart disease</td>
<td>1.8yr</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Asthma</td>
<td>4.5yr</td>
<td>12</td>
<td>0</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Anomalies respiratory</td>
<td>4mo</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>GE reflux</td>
<td>1.4yr</td>
<td>0</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>178 (80.9%)</td>
<td>25 (11.4%)</td>
<td>17 (7.7%)</td>
<td>220</td>
</tr>
</tbody>
</table>

Warning Signs

- Unexplained bronchiectasis.
- Unusual presentation of the infection.
- Dysmorphic features associated with recurrent infection.
- Infections worsening chronic disorders (asthma or seizure).
- Development of vaccine pathogen after vaccination (e.g., HiB infection despite previous HiB vaccine).
- Complication associated with live vaccination.
- Delayed umbilical cord separation.
- Unexplained autoimmune disease.
Screening for PID

Recurrent sinopulmonary tract infections
Encapsulated bacteria

Diagnosis consideration:
B cell/ antibody def, Complement, phagocytic def, WAS, HIV

Initial tests: CBC with differential count, IgG, IGA, IgM,
Specific antibody titers (Tetanus, HIB, Pneumococcal), CH50

Referring: if abnormal, or normal but problems persist
Screening for PID

Recurrent skin infections
Recurrent pyogenic infections

Diagnosis consideration:
B cell/ antibody def, Complement, phagocytic def, LAD, HIE

Initial tests: CBC with differential count, IgG, IGA, IgM, IgE
CH50, nasal swab culture

Referring: if abnormal, or normal but problems persist
Screening for PID

Failure to thrive, opportunistic/ fungal infections
Unusual or severe infections

Diagnosis consideration:
B cell/ antibody def, T cells defects & SCID, STAT1 deficiency, XLP, NEMO
IRAK4 def

Initial tests: CBC with differential count, IgG, IGA, IgM, IgE

Referring: All cases
Screening for PID

Autoimmune or chronic inflammatory disease
Lymphoproliferative diseases

Diagnosis consideration:
ALPS, XLP, IPEX, APECED, CVID, complement def

Initial tests: CBC with differential count, IgG, IGA, IgM, CH50
Autoantibodies, ESR, CRP

Referring: All cases, especially with infections
Transient Hypogammaglobulinemia in Infancy (THI)

- A prolongation of physiologic hypogammaglobulinemia

- Low IgG with or without low IgA and/or IgM beyond 6 months of age

- Most infants are able to respond normally to vaccine antigens

- Asymptomatic VS symptomatic

- Hypogammaglobulinemia may persist up to the age of 5 years.
Transient Hypogammaglobulinemia in Infancy (THI)

Clinical Features
• Recurrent sinopulmonary tract infections, recurrent diarrhea, prolonged oral candidiasis.
• Eczema, AR, food allergy
• Tonsils and lymph nodes are present.
• Mild neutropenia or thrombocytopenia
Transient Hypogammaglobulinemia in Infancy (THI)

Lab Features

• Low IgG beyond 6 months of age
• Normal or low IgA (1/2 of cases)
• Normal or low IgM (1/5 of cases)
• Normal protective antibody titers or non-protective or antibody titers (15% of cases) including low tetanus, HIB, pneumococcal titers

Dorsey MJ, Ann Allergy Asthma Immunol 2006
Transient Hypogammaglobulinemia in Infancy (THI)

Diagnosis

Require follow up and retesting with normal results.

- **Typical case**
  
  Low IgG, not profound hypogammaglobulinemia except premature

  Normal antibody titers

  Normal B (CD19), T (CD3/4/8), NK (CD3/4/8, CD56) cells

- **May have low IgG + Low IgA +/- Low IgM, +/- Low antibody titers and elevated B (CD19) cells**
Transient Hypogammaglobulinemia in Infancy (THI)

Treatment

- Observation, F/U Immunoglobulin level yearly
- Most THI will spontaneously resolve by age 4.
- Antibiotic prophylaxis
- IVIG is not indicated. A period of IVIG replacement may be considered.
Selective IgA Deficiency

Kutukculer N  Pediatr Allergy Immunol 2007
IgG Subclass Deficiency

Low Serum Immunoglobulin G, Levels in Infancy Can Be Transient

Aubert, A.; Reihman, N.D.; Chaoui, F.
6. A 2 year-old boy presents with recurrent sinus infections, low IgG, normal CBC, normal IgM, IgA, IgE, normal tetanus, HIB, pneumococcal titers and normal lymphocyte subpopulations (CD3, CD4, CD19, CD56).

Which one is the best recommendation?

A. Antibiotic prophylaxis  
B. IVIG replacement therapy  
C. Bone marrow transplantation  
D. Gene therapy  
E. Good hygiene, observation, recheck IgG in a couple years
7. A 6 year-old girl presents with left knee/ankle swelling and limping, no fever for 2 days. Yesterday, her mother noticed bruises on both legs. The patient had URI 2 weeks before limping. ROS is negative.

Which one is the most likely diagnosis?

A. Reactive arthritis
B. Septic arthritis
C. HSP
D. Leukemia
E. Hemophilia
Joint pain, not moving joint limping, pain on extremity

Is it arthritis?

Definition by ILAR* 2001

Swelling within a joint, or

Limitation in the range of joint movement with joint pain or tenderness observed by a physician, and not due to primarily mechanical disorders or to other identifiable causes.
Acute Arthritis: Overview

- A relatively common problem.
- Acute arthritis = any arthritis present < 6wks.
- A small proportion of children will go on to have chronic arthritis
Acute Arthritis: Overview

- A large proportion of acute arthritis
  - Self limiting
  - Symptomatic Rx for a short period of time.
- The challenge is to identify conditions requiring more than just symptomatic Rx.
Joint pain, not moving joint
limping, pain on extremity

Is it arthritis?

What are the possible causes?
Acute Arthritis: Overview

• The diagnosis requires
  - A good history including relevant ROS
  - A good knowledge of musculoskeletal exam
  - A good knowledge of conditions commonly associated with joint complaints.
## Joint complaints “ARTHRITEIS”

<table>
<thead>
<tr>
<th>A</th>
<th>Avascular necrosis and degenerative disorders: Perthes’ disease, Osteochondritis dissecan, Scheurermann’s disease, Slipped capital femoral epiphysis, Patellofemoral pain syndrome, Hypermobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Reactive arthritis: Post viral, poststreptococcal, postenteric infections</td>
</tr>
<tr>
<td>T</td>
<td>Trauma: Accidental and non-accidental (Child abuse)</td>
</tr>
<tr>
<td>H</td>
<td>Hematological: Leukemia, neuroblastoma, lymphoma, hemophilia, hemoglobinopathy</td>
</tr>
<tr>
<td>R</td>
<td>Rickets: Hypophosphatemic rickets, metabolic and endocrine disorders (Diabetes, Hypothyroidism)</td>
</tr>
<tr>
<td>I</td>
<td>Infections, Immunodeficiencies: Septic arthritis, osteomyelitis, tuberculosis, Brodie’s abscess, pediatric AIDS, common variable immunodeficiency (CVID)</td>
</tr>
<tr>
<td>T</td>
<td>Tumors of cartilage, bone, muscle: Benign (Osteoid osteoma, hemangioma, pigmented villonodular synovitis), malignancy (Osteosarcoma)</td>
</tr>
<tr>
<td>I</td>
<td>Inborn error metabolism, idiopathic pain syndromes</td>
</tr>
<tr>
<td>S</td>
<td>Systemic connective tissue diseases, Syndromes: SLE, Vasculitis (including HSP, Kawasaki disease), dermatomyositis, PAN, mixed connective tissue disease, Ehlers-Danlos syndrome, Down syndrome, Stickler’s syndrome</td>
</tr>
</tbody>
</table>
Acute Arthritis

- **Essential history**
  - Trauma and significant symptoms in 24-48hours
  - Swelling, limited ROM
  - Morning, Nocturnal symptoms
  - Duration
  - Constitutional symptoms
  - URI, diarrhea, dysuria, rash
  - Underlying diseases
  - Medications

- **Essential physical finding**
  - Joint swelling
  - Warm
  - Tenderness of jt line
  - Limited ROM
  - Red (Don’t routinely expect!!)
Joint pain, not moving joint
limping, pain on extremity

Is it arthritis

What are the possible causes?

Work Up
# Diagnostic Tests

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>CBC</td>
</tr>
<tr>
<td>ESR, CRP</td>
<td>ESR, CRP</td>
</tr>
<tr>
<td>ASO, Anti-DNaseB</td>
<td>ANA, RF</td>
</tr>
<tr>
<td>Liver enzyme</td>
<td>HLA-B27</td>
</tr>
<tr>
<td>BUN, Creatinine</td>
<td>FT4, TSH</td>
</tr>
<tr>
<td>U/A</td>
<td>U/A</td>
</tr>
<tr>
<td>Synovial fluid culture</td>
<td>Anti-dsDNA, anti-smith</td>
</tr>
<tr>
<td>Blood culture</td>
<td>C3, C4</td>
</tr>
<tr>
<td>Throat swab culture</td>
<td>ANCA</td>
</tr>
<tr>
<td>Urine culture</td>
<td>IgG</td>
</tr>
<tr>
<td>LDH, uric acid</td>
<td>CPK</td>
</tr>
<tr>
<td>ANA</td>
<td>PPD</td>
</tr>
</tbody>
</table>
Diagnostic Tests

• ESR:
  - Highly sensitive, low specificity
  - Normal ESR may be seen in JRA, SLE, systemic vasculitis, inflammatory muscle disease etc.
  - Be considered as an adjunct to a pt’s overall clinical status rather than an absolute reflection of disease activity.
## Diagnostic Tests

<table>
<thead>
<tr>
<th>False negative (Low ESR)</th>
<th>False positive (High ESR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agammaglobulinemia</td>
<td>Hypergammaglobulinemia</td>
</tr>
<tr>
<td>Afibrinogenemia</td>
<td>Hyperfibrinogenemia</td>
</tr>
<tr>
<td>Hyperviscosity state</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Anemia</td>
</tr>
<tr>
<td>Microcytosis, spherocytosis</td>
<td>Macrocytosis</td>
</tr>
<tr>
<td>High WBC</td>
<td>High ambient temperature</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td>Cachexia</td>
<td></td>
</tr>
<tr>
<td>Delay testing (&gt;2hrs)</td>
<td></td>
</tr>
</tbody>
</table>
Joint pain, not moving joint limping, pain on extremity

Is it arthritis

What are the possible causes?

Work Up

Treatment
Joint pain, not moving joint
limping, pain on extremity

Joint swelling

Yes

Right after injury/truama !!

Yes

Ortho consult

No

Limited ROM with joint pain & tenderness

Yes

# Joint involvement

Monoarticular

No

Polyarticular

Arthralgia/Periarticular

No
Joint Swelling

Knees
Joint Swelling

Knees
Joint Swelling

Ankles
Joint Swelling

MCPs
Limited Range of Motion
Limited Range of Motion

Shoulders
Limited Range of Motion
Joint Tenderness

MCP
Joint Effusion
Joint pain, not moving joint, limping, pain on extremity

Joint swelling

Yes

Right after injury/truma !!

Yes

Ortho consult

No

Limited ROM with joint pain & tenderness

Yes

# Joint involvement

Monoarticular

No

Polyarticular

Arthralgia/Periarticular

No

Yes
Acute Thigh Pain with Limping

An 8yo boy with fever for 5 days, anterior right thigh pain with limping for 3 days.
Acute Thigh Pain with Limping

Dx: Septic hip
Synovial Fluid Analysis

**Most helpful:**
- Differential count, leukocyte count,
- Culture, Crystal search (no need in kids)

**Less helpful:**
- Gram stain
- Glucose determination with simultaneous serum glucose
- Inclusion cells
- Mucin test
- Protein determination
- Lactic acid level

**Specific but rare findings:**
- LE cells
- Acid-fast organisms
- Giant cells
## Synovial Fluid Analysis

<table>
<thead>
<tr>
<th>Total WBC Count/mm³</th>
<th>%PMN</th>
<th>Appearance</th>
<th>Fluid Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-200</td>
<td>&lt;10%</td>
<td>Clear, viscous, pale, yellow</td>
<td>Normal</td>
</tr>
<tr>
<td>200-2000</td>
<td>&lt;20%</td>
<td>Clear to slightly turbid</td>
<td>Non-inflammatory</td>
</tr>
<tr>
<td>2000-50,000</td>
<td>20-70%</td>
<td>Slightly turbid</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>100,000 or more</td>
<td>&gt;70%</td>
<td>Turbid to very turbid</td>
<td>Septic arthritis</td>
</tr>
</tbody>
</table>
Acute Thigh Pain with Limping

A 13 YO boy with Rt thigh pain for 2 wks. The pain relieved by pills taken for 5 days. Limping was noted for 2 days.
Acute Thigh Pain with Limping

• US revealed no significant fluid in both hips with normal CBC, ESR. Naproxen was prescribed. A week after _ _ _ _ _

Dx: Transient Toxic synovitis
Monoarticular

Red

Yes ➔ Septic arthritis

No ➔ Recent Resp, GI infect

Yes ➔ RA, RS

RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DILE = Drug induced lupus
A 13 yo girl with swelling left knee and limping for 2 days. A history of sore throat 4 weeks ago and diarrhea 1 week ago was noted.

PE: Marked swelling left knee with warmth, painful limitation of movement.
Acute Right Knee Swelling

- Labs:
  - CBC: Hb 12, Hct 36% WBC 12,000, N65%, L35%, Eo2%, Mo8%
  - UA: normal
  - ESR 40
  - Synovial fluid analysis: WBC 85,000 PMN 80%, Mo20%
  - Synovial culture: Neg

Dx: Reactive arthritis
Monoarticular

Red

Yes

Septic arthritis

No

Recent Resp, GI infect

No

Constitutional symptoms

Yes

Malignancy

RA, RS

RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DILE = Drug induced lupus
Acute Right Knee Swelling and Weight Loss

A 5 YO girl with right knee pain at night for 1wk with weight loss 1 kg.
Acute Right Knee Swelling and Weight Loss

A 5 YO girl with right knee pain at night for 1wk with weight loss 1 kg.
Monoarticular

Red

Yes

Septic arthritis

No

Recent Resp, GI infect

Yes

RA, RS

No

Constitutional symptoms

Yes

Malignancy

No

Benign tumors

Early JIA

Hemophilia

RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DIL = Drug induced lupus
Right Knee Swelling with Limping

Dx: Monoarticular JRA

6 weeks after injection
Monoarticular

- Red
  - Yes: Septic arthritis
  - No: Constitutional symptoms
    - Yes: Malignancy
    - No: Benign tumors

Oligoarticular/ Polyarticular

- Recent Resp, GI infect
  - Yes: ASO, antiDNaseB
    - Positive: ARF
    - No: Early JIA

- No: Recent Resp, GI infect
  - Yes: Post strep RA
  - No: RA, RS

RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DIL = Drug induced lupus
RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DIL = Drug induced lupus
Acute Polyarthritis

A 7 YO girl presented with multiple joint pain & urticarial rash for 3 days and a history of diarrhea for 1 wk.
Acute Polyarthritis

1 day after naproxen started
**Monoarticular**

- Red
  - Yes: Septic arthritis
  - No: Recent Resp, GI infect
    - Yes: Constitutional symptoms
      - Yes: Malignancy
      - No: Benign tumors
    - No: Early JIA

- No: Constitutional symptoms
  - Yes: RA, RS
  - No: Post strep RA

**Oligoarticular/ Polyarticular**

- Recent Resp, GI infect
  - Yes: ASO, antiDNaseB
    - Negative: RA
    - Positive: ARF
  - No: Medications
    - Yes: SS DIL

RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DIL = Drug induced lupuse
## Drug-Induced Lupus (DIL)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>SLE</th>
<th>DIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>40-85</td>
<td>40-50</td>
</tr>
<tr>
<td>Arthralgias/arthritis</td>
<td>75-95</td>
<td>80-95</td>
</tr>
<tr>
<td>Myalgias</td>
<td>40-80</td>
<td>35-57</td>
</tr>
<tr>
<td>Rash</td>
<td>50-70</td>
<td>0-30</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>23-67</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>42-60</td>
<td>0-52</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>16-20</td>
<td>0-33</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>0-10</td>
<td>5-40</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>20-30</td>
<td>0-18</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>10-31</td>
<td>0-25</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>9-46</td>
<td>0-20</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>50</td>
<td>0-13</td>
</tr>
<tr>
<td>Neurologic involvement</td>
<td>25-70</td>
<td>0-2</td>
</tr>
</tbody>
</table>

Lahita RG, *SLE 3rd*
# Drug-Induced Lupus (DIL)

<table>
<thead>
<tr>
<th>Lab features</th>
<th>SLE</th>
<th>DIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>30-90</td>
<td>0-53</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>35-66</td>
<td>0-33</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20-50</td>
<td>0-10</td>
</tr>
<tr>
<td>+ Coomb’s test</td>
<td>18-30</td>
<td>0-23</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>50-70</td>
<td>60-93</td>
</tr>
<tr>
<td>ANA</td>
<td>&gt;95</td>
<td>100</td>
</tr>
<tr>
<td>Anti-histone</td>
<td>50-70</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>50</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>25</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Hypocomplementemia</td>
<td>40-65</td>
<td>0-25</td>
</tr>
<tr>
<td>RF</td>
<td>25</td>
<td>20-40</td>
</tr>
</tbody>
</table>

Lahita RG, SLE 3rd
## Drug-Induced Lupus (DIL)

<table>
<thead>
<tr>
<th>Drug definitively associated with drugs-related lupus:</th>
<th>Drug associated with drugs-related lupus:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline</td>
<td>Anti-TNF: Etanercept, infliximab</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Antiepileptic drugs: Valproate, carbamazepine, phenytoin, phenobarbital, ethosuximide</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Antibiotics: Penicilline, tetracyclines, streptomycin, nitrofurantoin, nalidixic acid, griseofulvin</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>NSAID: Ibuprofen, diclofenac, phenylbutazone, sulindac</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>B-blocker: Propranolol, atenolol</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Clonidine, cimetidine, enalapril, estrogen, PTU, spironolactone, sulfasalazine</td>
</tr>
</tbody>
</table>

Lahita RG, *SLE 3* ed
RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DIL = Drug induced lupus

**Monoarticular**

- Red
  - Yes: **Septic arthritis**
  - No: **Recent Resp, GI infect**
    - Yes: **Constitutional symptoms**
      - Yes: **Malignancy**
      - No: **Benign tumors**
    - No: **Early JIA**
      - Yes: **HSP, Vasculitis, SLE**
      - No: **Hemophilia**

- No: **Recent Resp, GI infect**

**Oligoarticular/ Polyarticular**

- Recent Resp, GI infect
  - Yes: **ASO, antiDNaseB**
    - Negative: **Post strep RA**
    - Positive: **ARF**
  - No: **Medications**
    - Yes: **SS DIL**
      - Yes: **Purpura**
      - No: **Hemophilia**
    - No: **RA, RS**
      - Yes: **Early JIA**
      - No: **Benign tumors**
Acute Left Ankle Swelling and Purpura
## HSP

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Organ involvement (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpable purpura</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>Edema</td>
<td>6</td>
<td>12.8</td>
</tr>
<tr>
<td>GI involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>35</td>
<td>74.5</td>
</tr>
<tr>
<td>Nausea/ vomiting</td>
<td>20</td>
<td>42.6</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>11</td>
<td>23.4</td>
</tr>
<tr>
<td>Renal involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated hematuria</td>
<td>13</td>
<td>27.7</td>
</tr>
<tr>
<td>Hematuria with proteinuria</td>
<td>5</td>
<td>10.6</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>Arthralgia or arthritis</td>
<td>20</td>
<td>42.6</td>
</tr>
</tbody>
</table>
Monoarticular

Red

Yes
No

Septic arthritis

Recent Resp, GI infect

Yes
No

Constitutional symptoms

RA, RS

Post strep RA

RA

ARF

SS DIL

Negative
Yes
No

Positive

Yes
No

Purpura

HSP, Vasculitis, SLE

Early JRA

Early JIA

Fever

Benign tumors

Malignancy

Hemophilia

Oligoarticular/ Polyarticular

Recent Resp, GI infect

Yes
No

ASO, antiDNaseB

Medications

Yes
No

RA = Reactive arthritis, RS = Reiter syndrome, SS = Serum sickness, DIL = Drug induced lupus
Oligoarticular/ Polyarticular with fever

Nocturnal pain

Yes

2-3 times elevated LDH

Yes

Suspect Malignancy

No

Normal/borderline low WBC/Plt

Yes

Suspect Malignancy
When to Suspect Malignancy

• Child appears miserable
• Pain and loss of function out of proportion to physical findings
• Night pain & Nocturnal awakening
• Periarticular bony tenderness rather than synovial tenderness
• Pain in both bones and joints
• Presence of petechiae/ecchymosis
• Hematologic abnormalities
• Elevated LDH, elevated Uric acid

Occult malignancy must be excluded.!!!!
Malignancy with Musculoskeletal pain

- Leukemia
- Lymphoma
- Neuroblastoma
- Histiocytosis
- Osteogenic sarcoma
- Ewing’s sarcoma
- Metastatic tumor (very rare)
When to suspect malignancy

The 3 most important factors predicting ALL
1. Low WBC (4,000)
2. Low-normal platelet count 150,000-250,000
3. Nighttime pain
All 3 factors: 100% sensitivity, 85% of specificity

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Predictive Value of Complete Blood Count Changes and Nighttime Pain for ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Marker</td>
<td>Blast-Negative ALL, n/N (%)</td>
</tr>
<tr>
<td>1 CBC parameter</td>
<td>41/52 (79)</td>
</tr>
<tr>
<td>2 CBC parameter</td>
<td>24/52 (46)</td>
</tr>
<tr>
<td>1 CBC parameter and nighttime pain</td>
<td>23/52 (44)</td>
</tr>
<tr>
<td>2 CBC parameters and nighttime pain</td>
<td>15/53 (29)</td>
</tr>
</tbody>
</table>

A Multicenter Case-Control Study on Predictive Factors Distinguishing Childhood Leukemia From Juvenile Rheumatoid Arthritis

May 2006
Oligoarticular/ Polyarticular with fever

Nocturnal pain

Yes

2-3 times elevated LDH

Suspect Malignancy

No

Normal/borderline low WBC/Plt

No

Low WBC/Plt

Suspect Malignancy

Yes

2-3 times elevated LDH

Work up for Infections, ASO, EBV, Parvo, ANA, ANCA

SoJRA

Negative

Positive

Dx based on the results
Systemic Onset JIA

- Arthritis in 1 or more joints with or preceded by fever of at least 2 weeks’ duration (“quotidian” for at least 3 days) and 1 or more of the following:
  - Evanescent (nonfixed) erythematous rash
  - Generalized lymph node enlargement
  - Hepatomegaly and/or splenomegaly
  - Serositis
Systemic Onset JIA

Quotidian fever, rash
Lymphadenopathy
HSM, serositis, arthritis
• NSAIDs
• Corticosteroid considered only for SoJRA
• Specific treatments
  – Penicillin and penicillin prophylaxis for ARF, PSRA
  – Cloxacillin or others for septic arthritis
  – HCQ, methotrexate for SLE
  – Chemotherapy/ cancer therapy
NSAID

Membrane phospholipids

Phospholipase A2

Arachidonic acid

Specific COX-2 inhibitors

“Classic” NSAIDs

COX-1

COX-2

Constitutive
“Protective” PGs
Stomach, Kidney,
Endothelium,
Platelets

Inducible
“Inflammatory” PGs
Joints

Constitutive
“Protective” PGs
Stomach, Kidney,
Endothelium,
Platelets

Inducible
“Inflammatory” PGs
Macrophages, joints,
cartilage, bone,
endothelium

NSAIDs

“Inflammatory” PGs
Joints

“Protective” PGs
Stomach, Kidney,
Endothelium,
Platelets

Paediatr Drug 2001: 3(11)
<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>JRA Trials</th>
<th>Doses (per day)</th>
<th>Dosage (mg/kg/day)</th>
<th>Max Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (81, 325mg)</td>
<td>Y</td>
<td>3-4</td>
<td>80-100</td>
<td>4900</td>
</tr>
<tr>
<td>Ibuprofen (200mg)</td>
<td>Y</td>
<td>3-4</td>
<td>30-50</td>
<td>2400</td>
</tr>
<tr>
<td>Diclofenac (25mg)</td>
<td>Y</td>
<td>3</td>
<td>2-3</td>
<td>150</td>
</tr>
<tr>
<td>Indomethacin (25mg)</td>
<td>??</td>
<td>3</td>
<td>1.5-3.0</td>
<td>200</td>
</tr>
<tr>
<td>Naproxen (250mg)</td>
<td>Y</td>
<td>2</td>
<td>10-20</td>
<td>1000</td>
</tr>
<tr>
<td>Meloxicam (7.5mg)</td>
<td>Y</td>
<td>1</td>
<td>0.25</td>
<td>15</td>
</tr>
<tr>
<td>Piroxicam</td>
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<td>1</td>
<td>5mg OD(15-30kg)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10mg OD(31-45kg)</td>
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<tr>
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<td></td>
<td>15mg OD(46-55kg)</td>
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</tr>
<tr>
<td>Celecoxib</td>
<td>Y</td>
<td>2</td>
<td>50mg BID (10-25kg)</td>
<td>N/A</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>100 mg BID (&gt;25kg)</td>
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</tr>
<tr>
<td>Toxicity</td>
<td>ASA</td>
<td>Ibuprofen</td>
<td>Naproxen</td>
<td>Indomethacin</td>
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<td>-------------------</td>
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<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>GI irritation</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CNS</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>+++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Hepatitis</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Asthma</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Renal function</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Bone marrow</td>
<td>-</td>
<td>+</td>
<td>+</td>
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</table>
7. A 6 year-old girl presents with left knee/ankle swelling and limping, no fever for 2 days. Yesterday, her mother noticed bruises on both legs. The patient had URI 2 weeks before limping. ROS is negative.

Which one is the most likely diagnosis?

A. Reactive arthritis
B. Septic arthritis
C. HSP
D. Leukemia
E. Hemophilia

C. HSP