Allergy, Immunology & Rheumatology Primer: Emergencies, Delayed Referrals, Perplexing Conditions
Edward G. Brooks, MD
Anthony J. Infante, MD, PhD
Pediatrics Grand Rounds
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Disclosures
- Dr. Brooks
  - Advisory board, research grant - United Allergy Services
  - speaker’s bureau - Merck

- Dr. Infante
  - speakers bureau, Baxter Bioscience (IVIG)

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- Office appraisal of allergy
- Emergency management of anaphylaxis
- Basic classification of angioedema
- Prompt recognition of SCIDS
- General approach to recurrent fever
- Common musculoskeletal pain syndromes

Allergic Rhinitis: symptoms
- Provoked by exposure to environmental allergens
- Common Symptoms:
  - Nasal, conjunctival pruritis
  - Sneezing, watery rhinorrhea, post nasal drip, lacrimation
  - Mucosal edema with nasal congestion / obstruction (mouth breathing, sleep disturbances)
  - Sinus ostial & eustachian tube dysfunction (midfacial pressure/pain, headache, ear pressure & occasional mild dizziness)
  - Diminished olfaction and taste

Allergic Rhinitis: physical signs
- Eyes:
  - conjunctivitis, Dennie’s lines, allergic “shiners”
- Nose:
  - edematous/pale/enlarged nasal turbinates, clear/mucoid rhinitis, polyps, transverse nasal crease from “allergic salute”
- Ears:
  - otitis media, retracted tympanic membrane from ET dysfunction
- Throat:
  - prominent lymphoid patches (cobblestoning), lateral pharyngeal bands

allergens
- Perennial (persistent) (mites, molds, pets)
- Seasonal (intermittent) (pollens)
Treatment of Allergic Rhinitis

- **Avoidance** – allergens and irritants (smoke, chemicals)
- **Antihistamines** - (pruritis, rhinorrhea)
  - azelastine, olopatadine
  - diphenhydramine (fast acting, sedating)
  - cetirizine, loratidine, fexofenadine
- **Corticosteroids**- topical (all symptoms)
  - mometasone, beclomethasone, fluticasone
- **Decongestants**- topical or systemic (congestion)
  - ephedrine, oxymetazoline (quick relief, rebound-Rhinitis Medicamentorum)
- **Anticholinergics**
  - ipratropium
- **Leukotriene Receptor Antagonists** (congestion)
  - montelukast
- **Cromolyn** (congestion)
- **Allergen Immunotherapy** (desensitization)

**Acute Bacterial Rhinosinusitis**

- Most often preceded by a viral URI
  - 0.5% to 2% of viral URIs (viral rhinosinusitis) develop into bacterial sinusitis (Berg, 1986)
- A [probable] diagnosis may be made if a viral URI has not improved after 10 days or has worsened after 5 to 7 days or if symptoms are out of proportion to a typical URI
- Common bacteria: *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*

**Most Rhinosinusitis Results From a Cycle of Mucosal Inflammation**

- **Mucosal Swelling**
  - (URI, allergy, environment)
- **Bacterial Infection**
- **Ostial Obstruction**
- **Mucous Stasis**
  - (antihistamines)

**Allergic Food Disorders**

- **IgE-Mediated**
  - Skin: Urticaria (urticaria)
  - Respiratory: Rhinitis, Asthma
  - Gastrointestinal: Oral allergy
  - Systemic: Anaphylaxis
- **Non-IgE-Mediated**
  - Atopic dermatitis, dermatitis herpetiformis
  - Heiner’s Syndrome
  - Celiac Dz.
  - Gastroesophageal reflux disease (GERD)
  - Enterocolitis, Enteropathy, Proctitis
  - Food-associated, exercise-induced anaphylaxis
Prevalence of IgE mediated reactions to foods in specific disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>FOOD ALLERGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>35-55%</td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td>37% in children, rare in adults</td>
</tr>
<tr>
<td>Urticaria</td>
<td>20% in acute, rare in chronic</td>
</tr>
<tr>
<td>Asthma</td>
<td>5-6% in children</td>
</tr>
<tr>
<td>Chronic Rhinitis</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Major Food Allergens

USA:
- Milk
- Egg
- Peanuts
- Tree nuts
- Seafood

France:
- Egg
- Peanuts
- Milk
- Mustard

USA:
- Milk
- Egg
- Peanuts
- Tree nuts
- Seafood

Australia:
- Milk
- Egg
- Peanuts
- Sesame seeds

Italy:
- Milk
- Egg
- Seafood

Diagnostic Approach

IgE-mediated acute symptoms
Tests positive - elimination diet
Tests negative-reintroduce (possibly as oral challenge)

Non-IgE-eosinophilic disorders
Elimination diet and oral challenges
Therapeutic intervention - steroids

Anaphylaxis definition(s):
1) the acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise or b) reduced blood pressure or symptoms of end-organ dysfunction
2) two or more of the following that occur rapidly after exposure to a likely allergen for that patient – involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms
3) reduced blood pressure after exposure to a known allergen

anaphylaxis

TABLE E1. Frequency of occurrence of signs and symptoms of anaphylaxis*%

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirtures</td>
<td>83-90</td>
</tr>
<tr>
<td>Urticaria and angioedema</td>
<td>45-55</td>
</tr>
<tr>
<td>Flushing</td>
<td>45-55</td>
</tr>
<tr>
<td>Pruritus without rub</td>
<td>2-5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>15-20</td>
</tr>
<tr>
<td>Dyspnea, wheezing</td>
<td>45-50</td>
</tr>
<tr>
<td>Upper airway angioedema</td>
<td>50-60</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>25-30</td>
</tr>
<tr>
<td>Dysuria, syncope, hyposthesia</td>
<td>30-35</td>
</tr>
<tr>
<td>Abdominal</td>
<td>6-12</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping pain</td>
<td>25-30</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5-4</td>
</tr>
<tr>
<td>Headache</td>
<td>4-6</td>
</tr>
<tr>
<td>Subternal pain</td>
<td>1-2</td>
</tr>
</tbody>
</table>

*On the basis of a compilation of 1835 patients reported in references. **IgE-mediated**

Therapy with H1 antihistamines work best for most patients with acute-types of short-lasting urticaria.
- Add H2 antagonists, montelukast if H1 antagonists do not suffice
- Steroids and other immunosuppressants should be reserved for chronic idiopathic urticaria, urticarial vasculitis, etc.
- **Urticaria - Physical Urticarias**
  - Physical urticarias (dermographism, cholinergic, cold)
  - Urticarial vasculitis
  - Chronic idiopathic urticaria
Angioedema

Urticaria – involving the superficial dermis
Most often characterized by intense pruritis due to histamine effect

Angioedema – involving deeper dermal and subcutaneous layers
May be pruritic but often characterized as a deeper and dull discomfort – burning quality

Laryngeal edema

Symptoms: dyspnea, chest pain, stridor, wheezing, throat tightness, dysphagia, drooling, anxiety
Usually responds to epinephrine (marginally in hereditary angioedema)

Angioedema - extremities

Symptoms: pain, swelling, nausea, vomiting
Often mistaken for acute abdomen
Chronic symptoms misdiagnosed as many conditions (celiac disease, GE, IBD, IBS)

Food-induced anaphylaxis

- Key foods: peanuts and tree nuts dominate (~90% of fatalities), fish, shellfish
- Frequency: ~ 150 deaths / year
- Clinical features:
  - Biphasic reaction – initially better, then recurs
  - Cutaneous symptoms may not be present
  - Respiratory symptoms prominent
- Risk factors:
  - Underlying asthma – Delayed epinephrine
  - Symptom denial – Previous severe reaction
  - Adolescents, young adults
- Most events occur away from home

Evaluation of suspected food-induced anaphylaxis:

- Positive skin prick test or specific IgE
  - Indicates presence of IgE antibody NOT clinical reactivity
  - ~90% sensitivity
  - ~50% specificity
  - ~50% false positives
  - Larger skin test/higher IgE correlates with likelihood of reaction but not severity
- Negative prick test or specific IgE
  - Essentially excludes IgE antibody (~95% specific)
Specific IgE Levels Associated with 95% Risk of Reaction
(detection limit = 0.10 or 0.35 kU/L)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Food</th>
<th>Serum IgE (kU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>Egg</td>
<td>≥ 7</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>Egg</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Child</td>
<td>Cow Milk</td>
<td>≥ 15</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>Cow Milk</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Child</td>
<td>Peanut</td>
<td>≥ 14</td>
</tr>
<tr>
<td>Child</td>
<td>Fish</td>
<td>≥ 20</td>
</tr>
</tbody>
</table>

Sampson H. J Allergy Clin Immunol 2004;113:805

Drug-induced anaphylaxis
- Penicillin (most common)
  - Cross reactivity with cephalosporins is low (<4% of PCN skin test positive subjects)
- Aspirin and NSAIDs 2nd most common
- Typically non-class-specific reactions
- Class-specific, non-immunologic (COX1 inhibition)
- Chemotherapy
  - Platinum agents very high (6-77% allergic reactions)
- Biologics – Xolair (0.2%), Rituximab, Remicade, etc.
  - “Humanized” mouse antibodies
- Radiographic contrast material (non-IgE mediated)

Insect Stings
- Anaphylaxis in 1% of children stung
  - Cutaneous local reactions very common
  - Systemic reaction in 5-10%
- Imported fire ants a common etiology for occult anaphylaxis
- Symptoms usually occur within minutes
- Local reactions do not predict a severe reaction; large local reactions/systemic are associated with slight increased risk
- Immunotherapy very effective

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Diagnostic testing
- Serum tryptase – levels peak 60-90 min. after onset and persist for 6 hours, special handling
- 24 hour Urinary methyl-histamine
- In vitro IgE testing
- Skin testing
- Challenge testing

Emergency treatment of anaphylaxis
- Epinephrine (0.01 cc/kg of 1:1000)
  - more rapidly anaphylaxis develops, the more likely the reaction is to be severe
- Anti-histamines – primarily short acting H1 antagonists (diphenhydramine)
- Corticosteroids – beneficial in asthma sx, and to prevent late-phase reactions
- Remain recumbent if hypotension present (fluid resuscitation)
- Observe for 4-8 hours
  - Indications for Extended Observation
    - Severe reaction of slow onset
    - History of previous biphasic reaction
    - Marked asthma sx component
    - Ingested antigen (continuous absorption)
- Discharge
  - Autoinjectable epinephrine
  - Anti-histamines for 24-48 hours
  - Corticosteroids for 24-48 hours
  - Education: avoidance of suspected causative agents
  - F/U allergy eval.

Respond Quickly!
- Administer epinephrine quickly
  - 0.3 cc (>30 kg, ~ 9 y/o )
  - 0.15 cc (15-30 kg)
- Activate EMS – 911
- Then, call emergency contacts
Pediatrics Grand Rounds
13 July 2012

University of Texas Health Science Center at San Antonio

Hereditary Angioedema (HAE)
- C1 esterase inhibitor deficiency
- 1:10,000 - 1:50,000
- Angioedema: face, extremities, gut, larynx, genitals/bladder/urethra
- Rash: serpiginous non-pruritic erythema (erythema marginatum?)
- NO URTICARIA

HAE C1INH C1INH func. C4
Type I low nl low
Type II nl low low
Type III nl nl nl

Anthony J. Infante, MD, PhD
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- Basic classification of angioedema
- Prompt recognition of SCIDS
- General approach to recurrent fever
- Common musculoskeletal pain syndromes

Case history
- 9 month old male infant
- Bronchiolitis/pneumonia/asthma at age 6 mos. responded to albuterol
- Repeat episodes at 7 mos. and now
- Breast feeding stopped at age 6 mos.
- Episode of oral thrush
- Exam: tachypnea, increased work of breathing, mild desaturation 90-95%

Previous lab and imaging results
- CBC on three occasions-normal total WBC, relative increased ANC, ALC 800-1500/mm^3
- Chest x-ray shows diffuse interstitial infiltrates

Immunology workup
- Lymphocyte subsets by flow cytometry
  - 50% CD19 (B cells)
  - 49% CD16/56 (NK cells)
  - 1% CD3 (T cells)
- IgM low, IgG and IgA undetectable
- Mitogen stimulation assay, specific genetic testing pending
- Prompt broncho-alveolar lavage or open lung biopsy

SCIDS: Definition
- Severe
  - Fatal if untreated
- Combined
  - Reduced numbers and/or function of both T and B cells
- Immune deficiency
  - Very reduced or absent immune function
  - Opportunistic and other serious infections
**SCIDS: Facts**
- Rare, est. 1 in 50,000-500,000 births
- 3:1 males: females
- Multiple underlying genetic defects
- Common presentations
- Life expectancy averages <2-3 years
- Potentially curable with stem cell transplant and/or gene therapy

**Clinical Presentations**
- Oral thrush
- Skin rash
- Potentially due to maternal engrafted T cells
- Failure-to-thrive
  - +/− diarrhea
- Opportunistic infections
  - CMV retinitis
  - Pneumocystis carinii pneumonia
  - Viral pneumonia
- Family history

**Laboratory clues to SCIDS**
- Lymphopenia
  - Especially lack of T cells
- B and NK cells may be decreased, normal or increased
- Lack of thymus on x-ray
- Hypogammaglobulinemia
- Decreased production
- Increased consumption

**SCIDS newborn screening**
- Planned addition to Texas NBS September 2012
- Analysis using dried blood spots
- DNA test for T cell receptor excision circles (TRECs) will detect most forms of SCIDS
- Initial and confirmatory testing
- TSDHS will advise referral to immunology specialist

**Case history**
- 3 year old girl with fever up to 41°C /105 F
- Stereotypical episodes lasting 3-5 days occurring every 4-6 weeks
- Multiply treated for pharyngitis, otitis media, and other minor infections
- Symptom-free between episodes
- Continues to grow and develop normally
- Exam during episode shows mild lymphadenopathy, one mouth ulcer

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> “SCID is a pediatric emergency. The average age at diagnosis is 6 1/2 months. If affected infants survive this long without a serious infection, they may be readily rescued with bone marrow transplantation...Once an infant is seriously infected, it becomes difficult, if not impossible, to intervene successfully. Thus it is of overriding importance to make the diagnosis of SCID early.”

F.S. Rosen, J. Peds., 1997
Infectious Etiologies of Acute Fever

- Viral syndromes - 50%
- Otitis media - 30%
- Serious infection (meningitis, pneumonia, UTI, etc.)
  - ER setting - 9%
  - Primary care setting - 1.3%

McCarthy, in Jenson & Baltimore, 2002

Determining Which Child Has Serious Infection

- Observation, history & physical exam have 86% sensitivity
- Observation
  - Alertness, irritability, consolability
- History, physical exam
  - Especially respiratory (pneumonia) and CNS (meningitis) findings

Nelson’s FUO definition

- Documentation by health care provider
- Without localizing signs or symptoms
- No diagnosis after 3 week evaluation as outpatient or 1 week as inpatient

Behrman et al. Nelson’s Pediatrics, 2004

Outcome of FUO workups

PFAPA syndrome

- Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis
- “Most common cause of regular fever pattern” (AAFP, 2003)
- First characterized as a distinct entity by Lawson et al. 1989
- Episodes seem to remit in late childhood without long term sequelae
- RX: antipyretics, steroids, colchicine

Samuels & Ozen, Curr. Opinion Rheumatol. 2006
Case history
- 15 y.o. female with chronic fatigue and pain “all over,” 18 months duration
- “A” student, former cheerleader, now has ceased all strenuous physical activity
- Naps during the day, falls asleep in class, takes 2-3 hours to fall asleep at night, does not awake refreshed
- Past history of “growing pains”
- Referred because of positive ANA, low titer

Case history cont’d.
- Review of systems “positive”- chest pain, abdominal pain, dysuria
- Treated variously with acetaminophen, ibuprofen, acetaminophen with codeine, tramadol, all with minimal improvement
- Exam-largely normal except for presence of multiple tender points

Interpretation of ANA
- ANA is sensitive because it is positive in virtually every patient with SLE, but it is not specific because patients with other autoimmune diseases frequently score positive
- Furthermore, approximately 5% to 15% of normal individuals have low titers of these antibodies, and the incidence increases with age.
- Antibodies to double-stranded DNA and the so-called Smith (Sm) antigen are virtually diagnostic of SLE but are much less sensitive (20-60%)


Fibromyalgia
- A common syndrome in which a person has long-term, body-wide pain and tenderness in the joints, muscles, tendons, and other soft tissues.
- Linked to fatigue, sleep problems, headaches, depression, and anxiety.


Symptomatology

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of People who Reported this Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower back pain</td>
<td>67%</td>
</tr>
<tr>
<td>Frequent headaches</td>
<td>47%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>40%</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>40%</td>
</tr>
<tr>
<td>Triggering</td>
<td>40%</td>
</tr>
<tr>
<td>Balance problems</td>
<td>40%</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>40%</td>
</tr>
<tr>
<td>Antiphospholipid</td>
<td>40%</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>40%</td>
</tr>
<tr>
<td>Swelling</td>
<td>40%</td>
</tr>
<tr>
<td>Depression</td>
<td>30%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>30%</td>
</tr>
<tr>
<td>Sinus problems</td>
<td>20%</td>
</tr>
<tr>
<td>Tooth disorders</td>
<td>20%</td>
</tr>
<tr>
<td>Restless legs</td>
<td>20%</td>
</tr>
<tr>
<td>Tinnitus (waking up in the ear)</td>
<td>30%</td>
</tr>
<tr>
<td>Jaw pain</td>
<td>30%</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>20%</td>
</tr>
<tr>
<td>Rashes</td>
<td>20%</td>
</tr>
</tbody>
</table>

Tender points
Fibromyalgia Cycle

- Muscle stiffness
- Depression
- Fatigue
- Limited activity

Treatment cycle

**Treatment**

- Aerobic exercise: at least 30 min. 5-6x/week
- Relaxation - yoga, biofeedback, meditation
- Improved sleep hygiene
- Physical and/or massage therapy
- Medications as adjunct therapy
  - Pregabalin (Lyrica)
  - Duloxetine (Cymbalta)
  - Amitriptyline

**Additional common causes of musculoskeletal pain**

- Osgood-Schlatter syndrome
- Patellar tendonitis
- Hypermobility
- Pes planus, genu valgum, etc.
- All are exacerbated by obesity!

**Referrals**

- Allergy, anaphylaxis, angioedema: Dr. Brooks
  - Misty Collett RN, 704-4504
- Immunodeficiency, fevers: Drs. Infante, Brooks
  - Viola Ortiz, 704-2187
- Rheumatology: Drs. Infante, Cole, Brooks
  - Patty Solis RN, 704-2963
- Consults, advice, etc.
  - Dr. Brooks, 567-5223
  - Dr. Infante, 567-0510
  - Stella Wise, 567-5250