Allergy, Immunology & Rheumatology Primer: Emergencies, Delayed Referrals, Perplexing Conditions
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Pediatrics Grand Rounds
August 23, 2013

Disclosures
- Dr. Brooks
  - Advisory board, research - United Allergy Services
  - Speaker's bureau - Merck
- Dr. Infante
  - Speakers bureau, Baxter Bioscience (IVIG)
  - Consultant, Luminex (SCIDS NBS)
  - Clinical trial, Merck (MMRV-AMP)

Learning Objectives
- Office appraisal of allergy
- Emergency management of anaphylaxis
- Basic classification of angioedema
- Newborn screening for SCIDS
- General approach to recurrent fever
- Common musculoskeletal pain syndromes

Edward G. Brooks, MD
- 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 and conjunctival pruritis
  - Sneezing, watery rhinorrhea, post-nasal drip, lacrimation
  - Nasal edema with nasal congestion or obstruction (mouth breathing, snoring)
  - Sinus ostial & eustachian tube dysfunction (medial 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, unclear/rhin mucoid rhinitis, polyps, transverse nasal crease
- Ears:
  - otitis media, ET dysfunction
- Throat:
  - prominent lymphoid patches (cobblesoning)
Inhalant allergens

- Perennial (persistent)
  - (mites, molds, pets)
- Seasonal (intermittent)
  - (pollens)

Allergic Rhinitis: treatment

- Avoidance – allergens and irritants (smoke, chemicals)
- Antihistamines - (pruritis, rhinorrhea)
  - azelastine, olopatadine
  - diphenhydramine (fast acting, sedating)
  - cetirazine, loradidine, fexofenadine
- Corticosteroids-topical (all symptoms)
  - mometasone, budesonide, fluticasone
- Leukotriene Receptor Antagonists (congestion)
  - Montelukast
- Anticholinergics
  - ipatropium
- Allergen Immunotherapy (desensitization)

Is it allergy or a URI?

- Fever
- Sore Throat
- Cough
- Nasal Drainage

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

Case history

- 13 y/o girl with repeated episodes of swelling and pain of face, hands, feet/legs, raised erythematous (non-pruritic) rash, throat tightness, abdominal pain and swelling
- Multiple family members with similar symptoms

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

The diagnosis and management of anaphylaxis practice parameter can be updated JACI notes
Anaphylaxis and angioedema

### Urticaria

**Acute Urticaria**
- Lasting 6–8 weeks or less
- Viral syndromes (especially in young children)
- Insect bites or stings (fire ants, bees, wasps)
- Food-induced reactions (eat this – get that)
- Medication-related (antibiotics, NSAIDs, narcotics)

**Chronic Urticaria**
- Lasting longer than 8 weeks

**Treatment of Urticaria**
- H1 antihistamines work best for most patients with acute types of short-lasting urticaria.
- Add H2 antagonists, montelukast
- Steroids and other immunosuppressants should be reserved for chronic idiopathic urticaria, urticarial vasculitis, etc.

### 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

### Angioedema - Extremities

### Angioedema - Gut

Symptoms: pain, swelling, N/V
- Often mistaken for acute abdomen
- Chronic symptoms often misdiagnosed as collagen disease, GI, IBD, IBS, etc.
**Allergic Food Disorders**

**IgE-Mediated**
- Skin: Urticaria, Angioedema, Dermatitis herpetiformis
- Respiratory: Asthma, Rhinitis
- Gastrointestinal: Anaphylaxis

**Non-IgE-Mediated**
- Skin: Atopic dermatitis
- Respiratory: Heiner's Syndrome
- Gastrointestinal: Celiac disease, Enteropathy, Proctitis

**Major Food Allergens**
- USA: Milk, Egg, Peanuts, Tree nuts, Seafood
- France: Egg, Milk, Peanuts, Mustard
- France: Egg, Peanuts, Tree nuts, Seafood
- Australia: Milk, Egg, Peanuts, Sesame seeds
- Sampson et al.

**Food-induced anaphylaxis**
- Peanuts and tree nuts dominate (~90% of fatalities), fish, shellfish
- Clinical features:
  - Biphasic reaction
  - Atypical presentation may occur
- Risk factors:
  - Underlying asthma = Delayed epinephrine
  - Symptom denial = Previous severe reaction
  - Adolescents, young adults
  - Most events occur away from home

**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

**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
- Chemotherapy
  - Platinum agents very high
- Biologics – Xolair (0.2%), Rituximab, Remicade, etc.
  - ‘Humanized’ mouse antibodies
- Radiographic contrast material (non-IgE mediated)

**Diagnostic testing**
- Serum tryptase – levels peak 60-90 min. after onset and persist for 6 hours, special handling
- 24 hour Urinary methyl-histamine
- Allergy testing/oral challenge
- Hereditary angioedema (HAE)
  - C1 esterase, C4

Allergy testing/oral challenge

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

<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>Cow Milk</td>
<td>≥ 15</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>Peanut</td>
<td>≥ 14</td>
</tr>
<tr>
<td>Child</td>
<td>Fish</td>
<td>≥ 20</td>
</tr>
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Emergency treatment of anaphylaxis
- Epinephrine (0.01 cc/kg of 1:1000)
  - 0.05 cc (15-30 kg), 0.3 cc (>30 kg, ~9 y/o)
- Anti-histamines
- Corticosteroids – beneficial in asthma sx, and to prevent late-phase reactions
- Hypotension: Recumbent, fluid resuscitation
- Observe for 4-8 hours

Indications for Extended Observation
- Severe reaction of slow onset
- History of previous biphasic reaction
- Marked asthmatic component
- Ingested antigen (continuous absorption)

Discharge
- Autoinjectable epinephrine
- Anti-histamines for 24-48 hours
- +/- Corticosteroids for 24-48 hours
- Education: avoidance of suspected cause

Case history
- 13 y/o girl with repeated episodes of swelling and pain of face, hands, feet/legs, raised erythematous (non-pruritic) rash, throat tightness, abdominal pain and swelling
- Multiple family members with similar symptoms
- No association with food ingestion
- No response to epinephrine, anti-histamines, steroids
- Serum tryptase and urinary methyhistamine negative

Hereditary Angioedema (HAE)
- 1:10,000 - 1:50,000
- Angioedema: face, extremities, gut, larynx, genitals/bladder/urethra
- Rash: serpiginous non-pruritic erythema (erythema marginatum?)
- NO URTICARIA
- Bradykinin mediated, not histamine/mast cell
- C1 esterase inhibitor deficiency
- Autosomal dominant, 25% spontaneous mutation, 11q12-q13.1

Case report
- 13 y/o girl with repeated episodes of swelling and pain of face, hands, feet/legs, raised erythematous (non-pruritic) rash, throat tightness, abdominal pain and swelling
- Multiple family members with similar symptoms
- No association with food ingestion or drug exposure
- No response to epinephrine, anti-histamines, steroids
- Serum tryptase and urinary methyhistamine negative
- C1 esterase inhibitor and C4 normal
- Elevated Factor XII during episodes
- Good response to weekly infusions of C1 esterase inhibitor and transexamic acid
Hereditary Angioedema (HAE)

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Case history
- Twenty-five day old, 34 week gestation infant with abnormal newborn screen for SCIDS x 2
- Mild respiratory distress
- CBC shows absolute lymphocyte count (ALC) of 136/mm³ (normal 2300-7000)
- CD3: 51; CD4: 43; CD8: 6; CD19: 11; CD16/56: 66

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
- Syndromes: a number of specific genetic defects with similar presentations

"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

Survival benefit from early treatment

Buckley, JACI 2012
Cost savings of early treatment

Buckley, JACI 2012

Other causes of abnormal SCIDS newborn screen
- Other immune deficiency states
  - DiGeorge syndrome
  - Ataxia-telangiectasia
- Other causes of T lymphopenia
  - Trisomy 21
  - Neonatal cardiac surgery with thymectomy
  - Neonatal leukemia
  - Lymphangiectasia, lymphangioma
- Severe prematurity

Case history
- 3 year old girl with fever up to 41°C /105.3°F
- Stereotypical episodes lasting 3-5 days occur usually 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

Infectious Etiologies of Fever
- Viral syndromes-50%
- Otitis media-30%
- Serious infection (meningitis, pneumonia, UTI, etc.)
  - ER setting-9%
  - Primary care setting-1-3%

Determining Which Child Has Serious Infection
- Observation, history & physical exam have 86% sensitivity
- Observation
  - Degree of alertness, irritability, consolability
- History, physical exam
  - Especially respiratory (pneumonia) and CNS (meningitis) findings

McCarthy, in Jenson & Baltimore, 2002
**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


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**Outcome of FUO workups**

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**PFAPA**
- 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


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**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

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**Case history cont’d.**
- Review of symptoms “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
- ANAs 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

Tender points

Fibromyalgia Cycle

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 tendinitis
- Hypermobility
- Pes planus, genu valgum, etc.
- All are exacerbated by obesity!

Referrals

- Allergy, asthma, anaphylaxis, angioedema: Dr. Brooks
  - Misty Collett, 704-4504
- Immunodeficiency, recurrent fevers: Dr. Infante
  - Viola Ortiz, 704-2087
- Rheumatology: Drs. Brooks, Infante, Cole
  - Patty Solis, 704-2993
- Consults, advice, etc.
  - Dr. Brooks, 567-5250
  - Dr. Infante, 567-0510
  - Stella Wise, 567-5250