Allergy and Immunology Pearls for the Internal Medicine Boards

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Allergy Immunology Pearls for the IM Boards

- Allergic Rhino-conjunctivitis
- Asthma
- Allergic Bronchopulmonary Aspergillosis
- Angioedema and Urticaria
- Anaphylaxis
- Adverse Drug Reactions/Desensitization
- Mastocytosis
- Common Variable Immunodeficiency

Allergic Rhino-conjunctivitis

- **Symptoms:**
  - Clear bilateral nasal discharge, sneezing, congestion (turbinates are pale and swollen), nasal and palatal itching, eye itching, redness, and clear discharge/tearing (conjunctivitis); palatal itching, ear blockage and itching.

- **Importance:**
  - Prevalence approximately 20%
  - Relationship between AR and asthma
    - In one study, 28% of patients with asthma had AR and 17% of patients with AR had asthma

  - Seasonal pollen from trees, grass, weeds
  - Perennial dust mites, cat/dog dander

- **Diagnosis:**
  - Prick/epicutaneous and intradermal skin test

**Treatment**

- Environmental Control/Allergen Avoidance *

- **Medications:**
  - Intranasal Steroids
  - Intranasal Antihistamine: Azelastin
  - Non-sedating antihistamines:
    - Loratidine, Desloratidine, Fexofenadine, Cetirizine, Levocetirizine
    - Decongestants: α adrenergic agonists
  - Mast cell Stabilizers (Cromolyn, Nedocromil)
  - Ocular Agents: Olpatidine, Ketotifen
  - Intranasal Anticholinergics (Ipratropium)

ASTHMA GINA guidelines 2009

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<tr>
<th>Step</th>
<th>Level</th>
<th>Medication</th>
<th>Failure</th>
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<td>Mild Persistent</td>
<td>Inhaled Steroids</td>
<td>No Improvement</td>
<td>Step 2: Moderate Persistent</td>
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<td>Combination Inhaled Steroids + Long-Acting β2-Agonists</td>
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<td>Step 2: Moderate Persistent</td>
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<td>Long-Acting β2-Agonists</td>
<td>No Improvement</td>
<td>Step 3: Severe Persistent</td>
<td>Severe Persistent</td>
<td>Combination Inhaled Steroids + Long-Acting β2-Agonists + Oral Steroids</td>
<td>No Improvement</td>
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<tr>
<td>Step 3: Severe Persistent</td>
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<td>Oral Steroids</td>
<td>No Improvement</td>
<td>Step 4: Very Severe Persistent</td>
<td>Very Severe Persistent</td>
<td>Combination Inhaled Steroids + Long-Acting β2-Agonists + Oral Steroids + Inhaled Corticosteroids</td>
<td>No Improvement</td>
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</tbody>
</table>

*Percentages in parentheses reflect percentage of patients. Preferred medications include: leukotriene receptor antagonists, anti-IgE, and monoclonal antibodies.

Disclosures

Schering Plough Consultant : ADR
Genentech: PI Xolair study
Asthma Severity

- IgE - Allergens
- Tobacco
- Rhinitis/sinusitis
- GER
- Medications (beta blockers)
- Viral respiratory infections (flu shot)
- Death prone asthmatics:
  - prior intubation
  - usage of bronchodilators
  - food allergies

Asthma and Aspirin sensitivity AERD

AERD Aspirin excerbated Respiratory Disease (Samter triad/tetrad)

- Asthma (steroid dependent)
- Nasal polyposis (loss of smell)
- Aspirin and NSAIDS intolerance (decreased FEV1>20% upon exposure)
- Chronic sinusitis

Management

- Leukotriene blockade (5-LO, LTR antagonist)
- Surgery (polyps, sinuses)
- Aspirin desensitization
- Part of the new classification of asthma endotypes (Lotvall JACI 2011)

Treatment: Allergic asthma Rhino-conjunctivitis

- Immunotherapy: Allergen Specific Vaccine
  - generation of Th 0 and T reg responses.
  - beneficial in randomized trials for pollen, alternaria, dust mites and cat allergens.
  - Subcutaneous (FDA) and oral route (USA trials)

Modified/Recombinant hypoallergenic proteins Chimeras (cat Fel d1/Fc)

- Anti-IgE: approved 3/2003 (omalizumab)
  - use in asthma NEJM 1999
  - moderate to severe persistent atopic asthma
  - FEV1 < 80%, specific allergen IgE

Allergic Bronchopulmonary Aspergillosis

Asthma/pulmonary infiltrates/central bronchiectasis

- Elevated total serum IgE >1000 ng/ml
- Peripheral eosinophilia
- Positive skin test and RAST (IgE) to Aspergillus
- Precipitins against Aspergillus
- Oral steroids, consider anti-fungals
- Association with cystic fibrosis and HLA DR2

Urticaria and Angioedema

- Urticaria
  - Acute < 6 weeks, Chronic > 6 weeks

- Urticaria:
  - pruritic geographic macular lesions with central clearing of short duration (<24h) and variable size

- Angioedema:
  - swelling ± pain, associated to urticaria in 40-50% of cases

Acute Urticaria

A cause is found in 20% of cases:

- Drugs: aspirin and NSAIDS
- Foods: egg, milk, peanut and nuts, seafood, shellfish
- Infections (viral/bacterial: HBV and HCV)
- Contact Allergies (animal dander and saliva; pollen from trees, grass, weeds)
Hereditary and Acquired Hereditary and Acquired

Cold-induced urticaria/chronic urticaria

Others:
- Corticosteroids
- Leukotriene antagonists
- Doxepin
- H2 antagonists
- H1 antagonists

(with and without asthma)

Plasmapheresis, IVIG, Levothyroxine
Hydroxychloroquine, Sulfasalazine, Cyclosporine, Hydroxychloroquine, Sulfasalazine, Cyclosporine,

Physical Urticarias
- Omalizumab Anti-IgE (Boyce 2007/ Kaplan 2009)

Connective tissue disorders:
- Hashimoto
- LES
- Elevated anti-peroxidase (TPO) and anti-microsomal antibodies, Graves disease
- Cryoglobulinemias
- Anti-bodies, Graves disease
- Autologous serum skin test positive (CIU index)

Cold, solar, aquagenic, vibratory

Exercise Induced

Pressure (delayed)

Symptomatic Dermatographism

Autoimmune
- Kallikrein inhibitor (Kalbitor, ecallantide, 10 mg sq X3)
- Purified C1inh (FDA 2009): Cinryze
- Bradykinin receptor 2 inh (Icatabant) 30 mg sq

Medical emergency caused by the acute release of epsilon amino caproic acid, tranexamic acid, FFP

androgenic steroids (danazol, stanazolol)

from antigen/ IgE activated mast cells

mediators from antigen/ IgE activated mast cells

involving and/or basophils, involving and/or basophils,

minutes, unless treated.

Anaphylaxis

Definition
Medical emergency caused by the acute release of mediators from antigen/ IgE activated mast cells and/or basophils, involving more than one organ system or presenting as laryngeal edema, which can lead to cardiovascular collapse, asphyxia and death in minutes, unless treated.

Symptoms
- Flushing/Pruritus/Urticaria/Angioedema
- Oropharyngeal and Laryngeal Edema (asphyxia)
- GI Colic, nausea, vomiting, diarrhea

Hypotension and cardiovascular shock

Complications: DIC, organ failure, seizures

Castells et al. In Allergy 3rd Ed 2005
Practice Parameters AAAAI 2007-2010
Anaphylaxis: Epidemiology

**Atopy, age, sex**

**Fatal Anaphylaxis:**
- **Asthma risk factor** Sampson NEJM, 1992
  - 0.002% for Penicillin
  - 0.001% for Hymenoptera (40 deaths/year)
  - Food-induced (peanuts, nuts)

**Non Fatal Anaphylaxis:**
- 1/2700 hospitalizations
- occupation (latex), repeated antigen exposure
  - 0.5% Hymenoptera Stings
  - 1/10,000 RCM Exposure
  - 1% PCN
  - 1/5,000-25,000 General Anesthetic Exposure
  - 1/3,000-5,000 Hemodialyses

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Causes of Anaphylaxis

**IgE /Mast Cell mediated**
- **Proteins:**
  - Foods: Peanuts, Nuts, Seafood, Eggs, Milk
  - Allergen Extracts
  - Hymenoptera Venom: Bee, Wasp, Jackets
  - Vaccines, antisera
  - Hormones (Progesterone Autoimmune Dermatitis), Enzymes
  - Monoclonal Abs : anti-TNFalpha, anti-CD20
  - Haptens: Penicillin, Platins,

**Complement mediated:**
- Dialysis membranes

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Non-IgE Anaphylaxis

**Direct Mast Cell/Basophil Activation**

- Radiocontrast Media
- Opiates, taxenes
- Anesthetics: Curare Derivatives
- Vancomycin (Red-Man Syndrome)
- **Arachidonic acid metabolism**
  - COX-1/COX-2 inh: aspirin and NSAIDS

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Anaphylaxis Diagnosis

**Acute:**
- Mediators:
  - Tryptase: total >11ng/ml, mature > 1 ng/ml
  - Histamine in 24h urine collection
  - Prostaglandin D2 metabolites in urine

**Hemoconcentration**
- Post-Capillary Venule Leakage

**Complement:** consumption (low CH50)
- Coagulation Cascade: activation (elevated PT/PTT, high Platelets)

**Retrospective:**
- **Antigen-Specific IgE**
  - A. RAST/CAP in serum (in vitro)
  - B. Skin Testing (in vivo)
  - C. Basophil activation FACS (Basotest: CD69/CD203)

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Serum Tryptase


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Fatal-Food Anaphylaxis: Risk Factors

- Previous Severe Anaphylaxis
- Asthma
- Allergy to: Peanuts, Tree Nuts, Fish or Shellfish (transgenic foods)
- **Patients on β-Blockers or ACE-inhibitors**
- Females ?
Latex Allergy Diagnosis

- **Risk Group**
  - Health Care Workers (OR, gloves, rubber devices, GI nozzles) (5-10%)
  - Rubber Industry Workers, Spina Bifida (18-28%)
  - Urogenital Abnormalities

- **Latex Associated Reactions and/or fruit reactions:**
  - Banana, Chestnut, Avocado, Kiwi, Mango, passion fruit, papaya and others: peach, watermelon, potato, tomato

- **Testing**
  1. RAST/CAP (38-82% sensitivity)
  2. Skin Test (>90% sensitivity): not in USA

Hymenoptera Sting

- **Natural History:**
  - 60% Re-sting reaction rate
  - The more severe the initial anaphylactic symptoms, the more likely there will be a re-sting reaction
  - The severity of the sting reaction is not related to the degree of skin test sensitivity or titer of serum venom-specific IgE
  - Patients with elevated baseline tryptase have associated mastocytosis

Risk of Systemic Reaction to Sting for VIT-Treated and Untreated Patients

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Acute Management of Anaphylaxis:

- **Epinephrine IM (not sq):** 0.3-0.5cc recumbent position, quadriceps
- **Adequacy of Oxygenation** (nebulized beta2 agonists), Cardiac Output and Tissue Perfusion
- **Anti-histamines H1 and H2 blockers:** 25-50 mg diphenhydramine po/IM or IV, ranitidine 150 mg
- **Steroids:** one single dose (IV or oral) to treat delayed, protracted anaphylaxis (6 to 24 hours after the initial event)

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Exercise Induced Anaphylaxis

**Associated with food allergy in >30% cases (wheat):**

- RAST, Skin Test Food

**Management:**

- Discontinue Exercise Earliest Symptom: Flushing, Pruritus
- Limit Exercise on Hot, Humid Days
- Avoid Exercise 4-6 hrs Post Prandial
- Avoid Exercise Post Allergy Immunotherapy
- Avoid Beta-Blockers and ACE Inhibitors
- Epinephrine: Prompt use
- Medi-Alert Bracelet

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Acute Management of Anaphylaxis in Adults

**If β Blockade:** Glucagon 5 - 15 μg/min I.V. Continuous Infusion
Observation for a Minimum of 6 Hours
At Discharge: Education, Allergy evaluation, Epi Pen

**ACE inhibitors** are implicated in severe and refractory anaphylaxis

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Golden, et al. JACI 2000

Practice Parameters AAAAI 2007-2010
Adverse Drug Reactions

Common Drugs:
- **PCN and related Abx:** IgE-mediated
  - Cross reactivity with cephalosporins (10% first generation, 1-2% 3rd-4th generation)
  - Aztreonam is non-crossreactive (except ceftazidime)
- **ASA and NSAIDs:** COX-1/COX-2 blockade, universal cross-reactivity
- **ACE-I:** Bradykinin-mediated
- **Sulfonamides:** no cross-reactivity with non-antibiotic medications (NEJM 2007)

Diagnosis:
- Skin test (Pre-Pen for PCN: FDA 2010)
- Challenge

Management:
- Avoidance, MediAlert Bracelets
- Desensitization (Antibiotics, Aspirin, Chemotherapy, Mo)

Non-IgE Hypersensitivity Reactions to Medications

- **DRESS syndrome:**
  - Eosinophilia, rash, systemic symptoms, LAD, LFT
  - Anti-convulsants: cross-reactivity is universal (phenytoin, phenobarbital, carbamazepine)
- **Delayed Maculopapular Rashes EM/SJS/TEN**
  - Sulfonamides, beta-lactams

Abacavir:
  - Fever, rash, systemic involvement, death
    - Genotyping HLA B57, skin testing

Quinolones:
  - Universal cross-reactivity

Standard desensitization protocol for IV desensitizations in 413 cases

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Total time = 411 minutes

Paclitaxel Desensitization

Feldweg A et al. Gyn Onc 2005

The New York Times Magazine

June 7th, 2009

- “Mommy, I am afraid”
- The mother, a 32 yow, was lying unconscious in a public bathroom in a pool of bloody stool after feeling hot, dizzy and a fluttering heart.
- She told the ER doctors that her only medical problem was occasional panic attacks, flushing and a rash.

Urticaria Pigmentosa

Solution 1
- 250 cc of 0.001 mg/ml

Solution 2
- 250 cc of 0.012 mg/ml

Solution 3
- 250 cc of 0.120 mg/ml

Solution 4
- 250 cc of 1.191 mg/ml

The mother, a 32 yow, was lying unconscious in a public bathroom in a pool of bloody stool after feeling hot, dizzy and a fluttering heart. She told the ER doctors that her only medical problem was occasional panic attacks, flushing and a rash.
**Systemic Mastocytosis**

**Diagnostic Criteria**

**Major Criteria:**
- multifocal infiltrates of 15 or more mast cells in bone marrow and/or extracutaneous organs

**Minor Criteria:**
- > 25% spindle shaped mast cells
- c-kit mutations (codon 816)
- aberrant expression of CD2 and CD25
- Tryptase >20 ng/ml

**Common Variable Immunodeficiency**

- Sinusitis (>2), Pneumonia (>2), UTI (>3-4), Deep seated infections
- Low IgG, IgA, IgM (<2 SD)
- Poor response to vaccines: Pneumovax, H.Influenza, Hepatitis
- Gammaglobulin replacement:
  - IVIG or SQ 400mg/kg q 3-4 weeks
    - (TACI defect, association with autoimmune diseases and lymphoma)

**Summary Pearls for the IM Boards**

- Allergic Rhino-conjunctivitis IT
- Asthma: ASA desensitization
- Allergic Bronchopulmonary Aspergillosis: IgE
- Angioedema and Urticaria: C4, TPO
- Anaphylaxis: TRYPASE
- Adverse Drug Reactions/Desensitization: Pre-Pen
- Mastocytosis: c-kit D816V mutation
- Common Variable Immunodeficiency: IgG

**Board Question**

- An 18 yo patient presents with an episode of angiodema of face and abdominal pain. Which test would be most appropriate:
  1. tryptase
  2. C4
  3. CT abdomen
  4. CBC

**Board Question**

- A 50 yo male with CAD presents to the ER with hypotension, tachycardia, SOB and generalized hives after a wasp sting. Evaluation and management will include:
  1. skin test to hymenoptera venom
  2. tryptase
  3. epinephrine
  4. immunotherapy

**Disclosures**

- Schering Plough Consultant: ADR
- Genentech: PI Xolair study