Allergy Testing

Ben Davis, MD, PhD
Learning Objectives

• Describe the role of patient history in directing an allergy evaluation
• Describe the role of allergy testing in the evaluation of a patient
• Discuss the advantages and limitations of different allergy testing methods
• Discuss the key factors in interpreting allergy testing results
Outline

• Identifying appropriate patients for an allergy consultation
• Overview of assessment of allergic disease
• Serological tests for specific-IgE antibodies
• Allergy skin tests
• Food allergy testing
• Insect allergy testing
• Contact Dermatitis: Patch Testing
Which Clinical Conditions Should be Referred to an Allergy Specialist?

- Allergy skin testing and specific IgE serology are effective tests for confirming sensitization in:
  - Eczema, acute urticaria, angioedema
  - Food allergy and eosinophilic gastroesophagitis
  - Rhinitis, otitis, conjunctivitis, sinusitis
  - Asthma, cough, dyspnea
  - Insect sting allergy
  - Drug allergy (some i.e., Beta-lactams and local anaesthetics)
  - Occupational allergy (some)
  - Anaphylaxis
Evaluation of the Patient with Allergy Symptoms: Why is Specific Allergy Diagnosis Important?

- Identify specific triggers
  - Allergic rhinitis
  - Asthma
  - Atopic dermatitis
- Specific allergen immunotherapy (is currently the only disease modifying treatment)
- Food allergy: may help determine likelihood of clinical allergy and possibly persistence & severity
Diagnostic Allergy Laboratory Tests

• Allergen-specific IgE (over 200 allergen extracts)
  – Aeroallergens: pollen (weeds, grasses, trees), epidermals, dust mites, molds
  – Ingested Allergens: foods
    – Molecular allergen specific IgE (component testing)
  – Injected Allergens: hymenoptera venoms, drugs
• Total Serum IgE
• Mast Cell Tryptase
• Patch testing
Assessing an Allergy

Clinical History:
- A thorough history is important!
- Obtain a careful history and reviewing all available medical records

Diagnosis:
- Based upon clinical history, the patient’s records, physical exam findings, clinical tests to support adverse drug reactions (skin testing)
- Referral to an Allergy Specialist may be indicated
Drug Allergy – Clinical Evaluation

What questions should you ask the patient?

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>CONDITION</th>
<th>REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>What caused the reaction?</td>
<td>Why were you taking it?</td>
<td>What was the reaction?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIMELINE</th>
<th>ONSET</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long ago did it happen?</td>
<td>Time to symptom onset?</td>
<td>Length of the reaction?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>OTHER MEDS</th>
<th>EXPOSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>How did you treat the reaction?</td>
<td>Were your taking any other Meds/OTCs at that time?</td>
<td>Have you taken same or similar medication since?</td>
</tr>
</tbody>
</table>

Allergy

When is it Suspected?

Symptoms are compatible with immune reaction

Temporal relationship between exposure and adverse event

The class/structure of the offending agent is associated with immune reactions

The patient previously encountered the offending agent

There is no other clear cause for the reaction

Skin tests or laboratory findings are compatible with hypersensitivity
Types of Hypersensitivity (Aka. Allergy)

**Gell and Coombs System**

**TYPE I**  
Anaphylactic (IgE-Mediated)  
- Allergen binds to IgE on basophils or mast cells, resulting in release of inflammatory mediators  
- Anaphylaxis, urticaria, angioedema, wheezing  
30 – 120 min

**TYPE II**  
Cytotoxic  
- Antigen-specific antibody to IgG or IgM initiates cell destruction  
- Hemolytic anemia, thrombocytopenia, interstitial nephritis  
>72 hrs to weeks

**TYPE III**  
Immune Complex  
- Antigen-antibody complexes form, deposit on blood vessel walls → activate complement system  
- Serum sickness-like syndrome  
>72 hrs to weeks

**TYPE IV**  
Cell-Mediated (Delayed)  
- Antigens caused activation of T lymphocytes → release of cytokines and recruit effector cells (ex. macrophages, eosinophils)  
- Contact dermatitis, Steven’s Johnson Syndrome  
>72 hrs
Allergy Skin Testing

• Skin testing remains the central test to confirm allergic sensitivity when it can be performed\(^1\)
• Skin testing is fast (15-30 minutes), safe, sensitive and a minimally invasive procedure which can be cost effective
• Skin testing is reproducible
• Skin testing has demonstrated good correlation with results of nasal challenge\(^2\) and bronchial challenges\(^3\)
• Results of skin test should always be used as an adjunct to the clinical history and physical examination when making the diagnosis of allergic disease

1. Oppenheimer et al, Ann Allergy 2006;S1:6-12
Diagnosis – Detection of allergen specific IgE
Greer Derma-Pik
Multi-Test II
Intracutaneous Tests (IDT)

- Useful for evaluation of anaphylaxis to drugs (penicillin, muscle relaxants) and venoms
- Use for ↑ sensitivity when SPT is negative despite convincing history
Clinical Sensitivity & Specificity of Skin Tests

• Prick skin tests may be positive in individuals who are without respiratory symptoms (high false positive rate).
• 29% -42% may have +SPT and no disease
• Always use caution when interpreting skin tests; skin tests are a confirmatory diagnostic tool reflecting sensitization and do not make the diagnosis of clinical allergy
• Diagnosis of clinical allergy = history and confirmatory allergy diagnostic tests.

Allergen-Specific IgE
InVitro (serum) and In-Vivo (skin tests)

<table>
<thead>
<tr>
<th></th>
<th>IgE Antibody</th>
<th>Skin tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sensitivity*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High specificity*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High reproducibility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Quantitative results in kIU/L^</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>WHO Standard calibrated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Quality assurance test program</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Can be used independently of pharmaceutical treatment</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Can be used independently of patient skin status</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Time factor</td>
<td>1-7 days</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td>Cost factor</td>
<td>more expensive</td>
<td>inexpensive</td>
</tr>
<tr>
<td>Usefulness in motivating patients</td>
<td>obscure</td>
<td>dramatic</td>
</tr>
</tbody>
</table>
Food Allergy

• True prevalence of IgE-mediated food reactions is 3-5%.
• Adverse reactions to foods in up to 25% of the population
  • Non-allergic adverse reactions include: intolerance (lactose intolerance), toxic effects (food poisoning), pharmacologic effects (caffeine)
• Non-IgE mediated food hypersensitivity reactions
  • Enterocolitis, enteropathy, proctocolitis
IgE Testing in Food Allergy

- Identifies sensitization but not intrinsically diagnostic of clinical reactivity
  - Modest sensitivity/specificity leads to false positive and false negative
  - FP ~ 20-50% of positive results.
- Patients incorrectly diagnosed as food allergic may adversely affect:
  - Quality of life
  - Nutritional status
  - Growth in children
- Clinical history guides the diagnostic work-up
- Confirm a food as a cause of a typical allergic reaction when food is a suspected trigger
  - e.g., urticaria, angioedema, wheezing, anaphylaxis proximate to ingestion (episodic)
  - **Same food is not tolerated after initial reaction.**
  - Rarely, to evaluate the role of foods in chronic disease: moderate-severe atopic dermatitis, eosinophilic gastrointestinal disorders.
Food Specific-IgE Antibody Concentrations or Skin Test Correlate with Risk of Clinical Reactivity

Only at certain high IgE values, the chance of a clinical reaction approaches certainty.

Negative test is not zero risk.
Office Based Evaluation of Food Allergy

• Primary Care Professional
  – Clinical history (symptoms, food, reaction consistency, alternative explanations, determination if likely IgE mediated)
  – Avoid indiscriminate “panels” of screening tests
  – Refer to Allergist

• Allergist
  – Apply “prior probability” (reasoning from the history) for test selection and interpretation
  – select tests to confirm/exclude suspicions
    – Serum and/or skin prick tests for food-specific IgE antibodies
    – avoid testing tolerated foods
    – Cross-reactivity (among foods/with pollen) may result in clinically irrelevant positive tests
  – Diagnostic elimination diets
  – Physician-supervised oral food challenges (gold standard)
Overview of Insect Sting Allergy

- Epidemiology:
  - systemic reactions in 3% of adults, 1% of children
- Pathogenesis
  - IgE antibodies cause 99% of systemic reactions
  - Venom-specific IgE antibody tests (skin and serum) – confirm diagnosis, clarify risk of future reactions, enable venom immunotherapy
- Treatment:
  - Venom immunotherapy prevents 98% of systemic reactions and induces long-lasting tolerance in 85%-95% of patients.
  - Decreases risk of future life-threatening venom reaction from >50% to <5%.
Insect Allergy: Importance of Patient History

- Patient History – chance of a dangerous reaction in future?
  - Large local reactions and cutaneous systemic reactions are not a risk for future sting anaphylaxis. But, anything more severe than this is. (Eg. wheezing, hypotension, two or more symptoms).
  - Risk of anaphylaxis can persist for decades with or without intervening stings
  - Reactions may not occur to one sting but may still occur to a later sting
Venom Allergy Testing

• Baseline tryptase indicated in patients with anaphylaxis
• Clinical significance – Depends on past history:
  – Positive skin or serum tests in >20% of normal adults
  – 70-90% of those with large local reactions, but they both have <5% risk of anaphylaxis
    – Unnecessary fear and avoidance of outdoor activities and/or unnecessary VIT
    – Exclusion from work or military service
  – Positive tests in 70-90% of those with previous anaphylaxis (who have >50% risk of anaphylaxis)
Patch testing

- Allergic contact dermatitis (ACD) is a T-cell-mediated, delayed-type hypersensitivity response to exogenous agents.
- The clinical diagnosis of ACD is based upon the lesion morphology and distribution.
  - Lesions consist of pruritic, erythematous, indurated, scaly plaques
  - Vesiculation and bullae may be seen in severe cases.
  - The involvement of hands, feet, eyelids, and lips, which most commonly come in contact with the environment, suggest the diagnosis of ACD.
- Patch testing occurs over 72 hour period.
# Beta-Lactam Drug Allergy

- Antimicrobials most commonly cause IgE-mediated reactions
  - Common for beta-lactam antibiotics (penicillins and cephalosporins)
  - *Penicillin is responsible for 75% fatal anaphylactic drug reactions*

<table>
<thead>
<tr>
<th>1-10%</th>
<th>10%</th>
<th>0.1-1%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERAL POPULATION</strong></td>
<td><strong>SELF-REPORTED</strong></td>
<td><strong>ACTUALLY HAVE A TRUE ALLERGY!</strong></td>
</tr>
<tr>
<td>Self-Report Beta-Lactam Allergy</td>
<td>Have a TRUE Allergy</td>
<td></td>
</tr>
</tbody>
</table>


Penicillin Drug Allergy - Amnesia

Penicillin-Specific IgE Decreases

Loss of Sensitivity

~10% Per Year

50% 5 YEARS

80% 10 YEARS

Cephalosporin Drug Allergy

**Cross-Reactivity**

Penicillin & Cephalosporins

- Share beta-lactam ring
- Cephalosporin rates 10x lower as directed at side chains
- Anaphylaxis may occur if history of penicillin allergy
- Before 1980, cross-reactivity was 10-20% as 1st generation cephalosporins were contaminated with PCN

**FACTS**

- 1st & 2nd generation most common
- Clinically rare

**2 PERCENT**

Chance of Reaction to Cephalosporin with Penicillin Allergy History

Take Home Points

• Timing of type I/IgE reactions are quick on/quick off
• Type I/IgE mediated reactions require a prior exposure
• Type I/IgE mediated reactions are consistent after the initial reaction.
• Allergy testing is used as adjunct to clinical history, alone they don’t diagnose allergy, only demonstrate a sensitivity.
  • High false positive rate
  • Avoid indiscriminate panels or screening tests.
• Most patients labeled penicillin allergic (~90%) are not allergic
  • 80% lose it in 10 years, ~100% lose it in 20 years.