Allergy Diagnostic Testing

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Objectives

- Review conditions that warrant allergy diagnostic testing
- Discuss allergy diagnostic testing
- Highlight pearls and pitfalls of allergy diagnostics
Disclosures

- None

Primary conditions that warrant allergy diagnostics

**IgE-mediated allergic disease:**
1. Allergic rhinitis
2. Allergic conjunctivitis
3. Allergic asthma
4. Food allergy
5. Insect venom (hymenoptera) allergy
6. Penicillin allergy

**Cell-mediated allergic disease:**
1. Allergic contact dermatitis
Questions to think about with testing:

1. Is this condition allergic (high pre-test probability)?

2. Will testing make a difference in treatment recommendations?

3. Should I order/perform the test or refer?

Allergic Rhinoconjunctivitis and Asthma
Oklahoma Allergies

Winter  Cedar Pollen
Spring  Tree pollens such as oak, pecan, mulberry
Summer Grass pollens such as Fescue, Bermuda
Fall   Weeds such as Ragweed, Pigweed, Trees such as cedar elm

Perennial  Indoor allergens, animals, molds
Pollen

Used by trees and plants for reproduction

Some trees/plants utilize insects for pollination

Other trees/plants utilize the wind for pollination
- High levels of light weight pollen are released into the air
- These pollens can be inhaled and lead to symptoms

Common Allergens

Mountain Cedar (Ashe Juniper)
- Common in Texas and Oklahoma
- Pollinate in late winter, early spring
- Small, gnarled tree
- Spreading aggressively
- Can trigger “cedar fever” or “cedar asthma”
Common Allergens

Ragweed

- Pollen occurs in late summer, fall
- Produces copious amounts of pollen
- Pollen is highly allergenic

Asthma Triggers: Allergy

Most children with asthma (>75%) have allergies to environmental allergens

When sensitized asthmatics are exposed to allergens:

- Increase in asthma symptoms
- Precipitate asthma exacerbations

Important questions include:

- Is exposure to the allergen associated with asthma symptoms?
- Is reduction of exposure possible?

Make sure to test for relevant allergens

Check local pollen counts (oklahomaallergy.com)
Include indoor allergens such as mites, roach, animals, mold
Food allergy does not cause isolated nasal/asthma symptoms

Consider testing modalities:
Skin Prick Testing
Skin Intra-dermal Testing
In-vitro Testing

### Allergy Testing Characteristics

<table>
<thead>
<tr>
<th>Assay</th>
<th>Allergen group</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgE assay</td>
<td>Inhalants</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Foods</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Venoms</td>
<td>++</td>
<td>+++</td>
</tr>
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</tbody>
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Allergy Diagnostics: ARC & Asthma

Based on history, there should be a high pre-test probability in those being tested.

For ARC & asthma, skin testing and in vitro tests have high positive and negative predictive values.

What are the test results going to be used for?
- Identification of allergic triggers?
- For counselling about avoidance of allergic triggers?
- To determine if patient needs referral to specialist?
- To determine if patient is candidate for immunotherapy?

Food Allergy
Food Allergy: Pathophysiology

Sensitization
- Antigen
- Dendritic Cell
- Peanut-Specific T cell
- Th1
  - IFN-γ
  - IL-4
  - IL-5
  - IL-13
- Th2
- B
- Mast Cell
- IgE

Re-exposure
- Immediate symptoms (<2 hrs) with each exposure such as itching, urticaria, angioedema, n/v/diarrhea, sob/wheezing, hypotension, anaphylaxis

IgE-mediated Food Allergy

- Public perception of food allergy: 25 – 30%
- True prevalence of IgE-mediated food allergy:
  - 2-4% of adults
  - 4-6% of children
- Parent perception of food allergy in child with AD: very high
Most food allergy is caused by 8 foods

TABLE I. Estimated food allergy rates in North America

<table>
<thead>
<tr>
<th>Allergen group</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>2.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Egg</td>
<td>1.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Peanut</td>
<td>1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Fish</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Shellfish</td>
<td>0.1%</td>
<td>2%</td>
</tr>
<tr>
<td>Wheat, soy</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Sesame</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>5%</td>
<td>3% to 4%</td>
</tr>
</tbody>
</table>

Sicherer, J Allergy Clin Immunol, 2010

Allergy Testing Characteristics

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Allergy Diagnostics For Food Allergy

In-vitro tests AND skin testing have high sensitivity and low specificity

They do a good job at ruling out IgE-mediated food allergy, but when positive (measurable specific IgE), they have a low positive predictive value

CONSEQUENTLY, ONLY TEST FOODS THAT HAVE A HIGH PRE-TEST PROBABILITY (AND THAT IS BASED ON HISTORY!)

Food Allergy: Diagnosis

History and physical
   Food in question (protein)
   Symptoms
   Timing
   Reproducibility
   Treatment
   Outcome

Skin testing

Serum food-specific IgE testing

ONLY for evaluation of IgE-mediated symptoms
Food Allergy Diagnostics

Serum food-specific IgE levels and skin testing both detect the presence of IgE

**Presence of IgE ≠ clinical allergy**

Tests should not be viewed as positive or negative

Instead, tests indicate the probability of a clinical reactivity

Larger the SPT or higher the IgE level → indicates higher probability NOT severity

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Effect on probability of clinical allergy for a food-specific IgE level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of immediate reaction to food in question</td>
<td>Supports clinical relevance of detected IgE</td>
</tr>
<tr>
<td>Younger Age</td>
<td>Lower levels of specific IgE have increased clinical relevance in young children</td>
</tr>
<tr>
<td>African-American</td>
<td>Associated with higher levels of specific IgEs with decreased clinical relevance</td>
</tr>
<tr>
<td>Eczema</td>
<td>Increased polyclonal IgE can be non-allergen specific and decrease clinical relevance</td>
</tr>
<tr>
<td>Inhalant allergy</td>
<td>Pollen sensitization can cause clinically irrelevant positive results to foods due shared epitopes</td>
</tr>
<tr>
<td>Hx of atopy</td>
<td>PPV of a specific IgE level increases with increased prevalence of the disease in the population</td>
</tr>
</tbody>
</table>

Case:
A 3 year old male with eczema ate a meal consisting of scrambled eggs and a glass of milk. No other foods eaten. He previously drank only soy milk and never ate straight eggs. (Family has always avoided cow’s milk due to older sibling with IgE mediated allergy to cow’s milk). He eats peanut butter daily without symptoms.
Within 5 minutes he developed widespread urticaria, lip angioedema and vomiting. He was treated for an allergic reaction and later his PCP ordered the following labs:

- IgE egg white = 7 kU/L
- IgE cow’s milk = 11kU/L
- IgE peanut = 12kU/L

Based on the history, would you have ordered all of these tests?
What additional questions would you have about his cow’s milk avoidance?
Based on the allergy testing, which food is he most likely to be allergic to?

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Decision Points: IgE Levels Associated With 95% Risk of Reaction

<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>

Garcia-Ara C, et al. J Allergy Clin Immunol 2001;107(1);185-90
Interpreting CAP-FEIA Levels

![Graph showing Peanut IgE Levels]

Increasing probability of clinical reactivity with increasing level of food-antigen specific IgE value; note: values <0.35 do not exclude allergic reactivity

Sampson HA. Update on Food Allergy. J Allergy Clin Immunol. 2004

Case:

Patient has high likelihood of being allergic to egg and milk.

However, patient has peanut sensitization (presence of peanut specific IgE), but patient is NOT clinically allergic to peanut.

Peanut should NOT be removed from the diet.

When unclear, consider referral for further testing and food challenges to determine tolerability to foods.
Leap Study\textsuperscript{1}: General Overview

640 infants with severe eczema &/or egg allergy were randomized to either eat OR avoid peanuts until age 5

Subjects were enrolled between ages 4-11 months and were not clinically allergic to peanut at time of enrollment (skin testing, oral challenges)

At age 5 years, subjects underwent oral food challenges with peanut to determine if clinically allergic to peanut

Conclusion: The early introduction of peanuts in this high risk cohort (severe eczema, egg allergy) significantly reduced likelihood of developing peanut allergy


AD and Food Allergy: It’s complicated

Rarely is food allergy the primary cause of AD

Approximately 30% of children under age 5 with moderate-to-severe eczema have allergy to 1 or more foods (vs 4-6% of general pediatric population)

Food allergy rarely contributes to atopic dermatitis in adults
**AD and Food Allergy: It’s complicated**

Food allergy can be considered with AD in 2 settings:

1. Immediate allergic symptoms with ingestion of suspected food allergen

2. Children under age 5 with moderate-to-severe eczema not responding to standard treatment

- NIAID Food Allergy Guidelines, JACI 2010

**Food Allergy Diagnostics: Pitfalls in AD**

Retrospective chart review of 125 children with AD who had in-vitro allergy testing to foods with subsequent food avoidance

89% of food challenges (325 of 364) were negative

The vast majority of foods that had been restricted were returned to the diet

In the absence of anaphylaxis, serum food-specific IgE testing cannot reliably be used to determine the need for a food elimination diet, especially in children with atopic dermatitis

Food Allergy Diagnostics: Take-home points

What does all this mean?

Panels of foods for IgE testing → Should be avoided!

Be selective in food IgE testing → Let the clinical history be your guide

If performing “screening IgE tests” in a small child with moderate to severe persistent eczema not responding to standard therapy, make sure to only test foods that are likely to cause allergy in that age group (avoid testing corn, chocolate, coffee, etc)

Beware of clinically irrelevant positives (sensitization)
Leads to unnecessary food restriction which can actually lead to development of life threatening food allergy
Inattention to basic skin care
Failure to thrive
Unnecessary patient and caregiver stress

Insect Venom Allergy
### Classification of Insect Sting Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Immediate, local, transient</td>
</tr>
<tr>
<td>Large local</td>
<td>Delayed, prolonged, progressive</td>
</tr>
<tr>
<td>Systemic</td>
<td>Immediate, generalized</td>
</tr>
<tr>
<td>Other</td>
<td>Toxic, serum sickness, neuropathy</td>
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### Indications for Stinging Insect Testing and Immunotherapy

<table>
<thead>
<tr>
<th>Classification of Sting Reaction by History</th>
<th>Venom Skin Test</th>
<th>Immunotherapy</th>
</tr>
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<tbody>
<tr>
<td>Large local</td>
<td>Not indicated</td>
<td>No</td>
</tr>
<tr>
<td>Systemic (cutaneous)</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic (mod-severe)</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic (cutaneous)</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Systemic (mod-severe)</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Children &lt;16 years</td>
<td>Generally not indicated</td>
<td>No</td>
</tr>
<tr>
<td>Toxic</td>
<td>Not indicated</td>
<td>No</td>
</tr>
</tbody>
</table>

1Middleton, 7th edition

2Systemic reactions limited to the skin account for approximately 60 percent of all systemic reactions to venom in kids and there is only a 10 percent chance of a future systemic reaction

*Middleton, 7th edition*
Insect Venom (hymenoptera) Allergy

Testing available for: fire ant, honeybee, hornets, wasp, yellow jacket

Test those with history of acute generalized reaction / anaphylaxis to identify allergy and if positive to offer allergen immunotherapy

Venom IT can reduce risk of future anaphylaxis from 40-60% to <5%

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Insect Venom Allergy Testing

As venom allergy can be life threatening, we want the allergy test to be highly sensitive to be able to rule out allergy.

Of the testing modalities available, intra-dermal testing has the highest sensitivity.

Skin testing is therefore the recommended initial way to evaluate for possible insect venom allergy (unless there is a medical reason for in-vitro testing instead).

Penicillin Allergy Testing
Penicillin Skin Testing

- Penicillin skin testing has been validated for IgE-mediated reactions.

- Penicillin skin testing is **NOT** performed to evaluate for other types of reactions (serum sickness, blistering reactions, anemia, nephritis, etc).

- Skin testing is rapid, sensitive and cost effective

- Penicillin skin testing is an important tool for antibiotic stewardship

- The negative predictive value of a negative penicillin skin testing is very high but not 100%, so oral challenges are typically performed to confirm tolerability
Allergic Contact Dermatitis

Pathophysiology of ACD

- Most contact allergens are small reactive molecules typically <500 Da
- Haptens must conjugate with epidermal and dermal molecules to become clinically relevant allergens
- Following skin barrier disruption, foreign antigens are taken up by dendritic cells/antigen presenting cells and travel through afferent lymphatics to regional skin draining lymph nodes
- Antigen presentation with subsequent activation of naïve T cells
- Once activated, these T cells express activation molecules which allow them to leave the lymph nodes and enter skin when re-exposed to the allergen

Contact Dermatitis 2011. Jeanne Duus Johansen, Peter J. Frosch, Jean-Pierre Lepoittevin
Positive patch test reaction to lanolin at 48 hours (dense perivascular infiltrate of mononuclear cells seen by Hematoxylin–eosin–saffron stain). Contact Dermatitis 2011. Jeanne Duus Johansen, Peter J. Frosch, Jean-Pierre Lepoittevin

When to consider ACD?

Consider ACD when patients have erythematous papules, vesicles or eczematous rash with crusted lesions especially when localized or fail to respond to treatment

Physical exam cannot always reliably distinguish between ACD and ICD

Differential diagnosis: ICD, atopic dermatitis, seborrheic dermatitis, dyshidrotic eczema, psoriasis, dermatitis herpetiformis, MF, etc.

ACD can coexist with other conditions such as atopic dermatitis
Sources of contact allergens

Airborne exposure (plant/botanical sources)
Direct application by personal care products
- Soap
- Lotion
- Shampoo
- Jewelry/metal/clothing

Ectopic transfer of the allergen
- Transferred from other body site
- Nail glues
- Hair products

Connubial contact dermatitis

Systemic contact dermatitis
- Nickel, BOP, Gold, Mercury, Cobalt, Al, Chromium, Zinc, Propylene glycol

Common Contact Allergens

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Positive Reaction %</th>
<th>Allergen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.5</td>
<td>Nickel</td>
</tr>
<tr>
<td>2</td>
<td>8.7</td>
<td>Neomycin</td>
</tr>
<tr>
<td>3</td>
<td>8.5</td>
<td>Fragrance mix 1</td>
</tr>
<tr>
<td>4</td>
<td>8.3</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>5</td>
<td>7.2</td>
<td>BOP</td>
</tr>
<tr>
<td>6</td>
<td>6.2</td>
<td>Cobalt</td>
</tr>
<tr>
<td>7</td>
<td>5.8</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td>8</td>
<td>5.8</td>
<td>Quaternium</td>
</tr>
<tr>
<td>9</td>
<td>5.5</td>
<td>P-phenylenediamine</td>
</tr>
<tr>
<td>10</td>
<td>4.7</td>
<td>Fragrance mix II</td>
</tr>
</tbody>
</table>

### Common causative allergens by site

<table>
<thead>
<tr>
<th>Location</th>
<th>Source</th>
<th>Allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>Cosmetics, plants, ectopic transfer</td>
<td>Pollen (compositae), fragrance, BOP, methacrylates, tosylamide/formaldehyde</td>
</tr>
<tr>
<td>Scalp/Neck</td>
<td>Cosmetics, hair products, hair dye, jewelry</td>
<td>Paraphenylenediamine, cocoaamidopropyl betaine, fragrance, BOP, formaldehyde/FR</td>
</tr>
<tr>
<td>Hands</td>
<td>Lotion, cosmetics, gloves</td>
<td>Formaldehyde/FR, fragrance, rubber chemicals (thiurams, carbamates), topical antibiotics</td>
</tr>
<tr>
<td>Anogenital</td>
<td>Topical medications, topical analgesics, cleaning/soothing wipes</td>
<td>Topical steroids, fragrance, MI/MCI</td>
</tr>
<tr>
<td>Feet</td>
<td>Shoes</td>
<td>Carbamates, thiurams, chromates</td>
</tr>
<tr>
<td>Legs</td>
<td>Lotions, medications</td>
<td>Fragrance, BOP, topical antibiotics, topical steroids, lanolin</td>
</tr>
</tbody>
</table>

### Allergy Diagnostics: Patch Testing

- Patches remain adherent to skin for 48 hours, then removed and evaluated for a reaction.
- Testing site is read again at 96 hours to determine if positive (evidence of T cell infiltration at test site).
SUMMARY OF ALLERGY DIAGNOSTICS FOR IGE MEDIATED DISEASES

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Questions?