Allergy Testing for Allergic Rhinitis

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Grand Rounds Presentation
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Overview

- History of allergy testing
- Allergic rhinitis
  - Definition
  - Diagnosis
  - Pathophysiology
  - Medical management
- Allergy testing for the Otolaryngologist
History of allergy testing

- 1872 pollen was identified as the causative factor for fall hay fever. Blakely performed first skin test with pollen extract.
- 1912 intradermal test by Schloss
- 1920’s skin prick testing introduced by Lewis and Grant.
- 1935 Hansel began using serial dilution testing (1:5 dilution with endpoint testing) and Rinkel perfected serial endpoint testing in the 1940’s
- Krouse modified quantitative testing
Allergic Rhinitis

- Inflammation to the mucosal lining of the nose caused by inappropriate hypersensitivity reaction to an aeroallergen.
- IgE mediated immune response, with mast cell activation and release of cytokines
Affective rhinitis

- Affects approximately 1/3 of US citizens
- Causes significant morbidity
- Lost work/school days
- Decreased productivity
- Costs of continued medication
Symptoms

- Rhinorrhea
- Cough/sneezing
- Nasal congestion
- Post nasal drip
- Nasal pruritus
- Watery eyes
- General fatigue
- Diminished quality of life
Types of AR

- Seasonal
  - Usually pollens, and outdoor molds

- Perennial
  - Caused by indoor allergens i.e. cockroach, dust mite, pets, and certain molds

- Episodic

- Occupational
History

- Onset, timing, duration, seasonality, severity, associated symptoms, aggravating/alleviating factors
- Thorough environmental history
- Family history of atopy
- Suspected allergens
- Nasal trauma
Physical

- General appearance
  - Allergic shiners, allergic salute, malaise
- Nose
  - Septal deviation, polyps, drainage, turbinate hypertrophy, hyponasality
- Mouth
  - Cobblestoning of oropharynx
- Ear
  - Middle ear pathology
- Neck
  - Lymphadenopathy, thyroid enlargement
- Chest
  - Wheezing
- Skin
  - Eczema, dermatographism
Differential Diagnosis

- **Non-allergic rhinitis**
  - Infectious, NARES, vasomotor rhinitis, atrophic rhinitis, drug induced, hormonally induced, exercise, reflex

- **Structural/mechanical factors**
  - Septal deviation, turbinate hypertrophy, adenoid hypertrophy, foreign body, tumor

- **Inflammatory/immunologic**
  - Wegener’s, sarcoidosis, midline granuloma, SLE, Sjogren’s

- **CSF rhinorrhea**
Atopic individuals inherit tendency to produce IgE-mast cell TH2 lymphocytic response.

With low level exposure to antigen, the antigen is taken up by APC (antigen presenting cells).

Antigen is processed, and epitope is expressed on the cell surface by MHC II.
CD4+ cells interact with APC’s and release cytokines IL3, IL4, IL5, and GM-CSF. These promote IgE production by plasma cells, mast cell proliferation and infiltration into nasal mucosa, and eosinophilia.
**Pathophysiology**

- **Early response** – IgE coated mast cells recognize allergens in the mucosal lining, and undergo degranulation.

  Preformed histamine, heparin, tryptase, kininogenase, and chymase cause the initial damage.

  Newly formed mediators include leukotrienes and prostaglandins. They are produced by breakdown of phospholipid cell membrane. These cause vessels to leak leading to watery rhinorrhea, nasal edema/congestion, and sneezing/pruritis.
Pathophysiology

- **Late response** – mast cells also secrete chemokines that promote VCAM, and E-selectin expression on endothelial cells. These allow other leukocytes to attach, and migrate into tissues. IL-5 is a potent chemoattractant of eosinophils, T lymphocytes, and macrophages. Over the course of 4 to 8 hours, these cells release their contents, causing further inflammation.
Management

- Environmental measures should be taken to avoid or decrease exposure to suspected allergens.
- Medical management with nasal steroids, decongestants, mast cell stabilizers, leukotriene receptor antagonists, or anti-IgE globulin
- Immunotherapy
Immunotherapy

- Immunotherapy has been shown to be efficacious in treating allergic rhinitis, asthma, and hymenoptera allergy.
- It is relatively safe. Severe anaphylactic reactions are rare in the U.S. after appropriately administered allergen immunotherapy.
- Li, JT et al. Annals of Allergy Asthma and Immunology Vol. 90, 2003
Immunotherapy

- Successful immunotherapy is associated with:
  - Shift from TH2 to TH1 lymphocyte immune response to allergen
  - Immunologic tolerance – decline in allergen specific responsiveness
  - Increases in allergen specific IgG blocking antibody
  - Relationship between efficacy and specific IgE titers are variable
Immunotherapy

- In patients with allergic rhinitis, must have symptoms of AR after natural exposure to aeroallergen, demonstrable evidence of clinically relevant specific IgE antibodies and one of the following:
  - Poor response to pharmacotherapy or allergen avoidance
  - Unacceptable adverse side effects to medications
  - Coexisting AR and asthma
  - Possible prevention of asthma in children
  - Desire to avoid long-term pharmacotherapy
Immunotherapy

- In order to mix the immunotherapy vaccine, specific allergens must be known.
- Vaccine should use standardized extracts.
- Immunotherapy requires a compliant patient, due to its long duration.
- Providers need to be prepared to handle patient with anaphylaxis.
Types of immunotherapy

- **Injectable vaccine** – mainstay of therapy in the US

- **Sublingual** - used widely in Europe
  - Wilson et al (2005) performed Cochrane database meta analysis 22 RCT, found therapy works, but difficult to compare with injection immunotherapy. Grade B

- **Intranasal** - currently under investigation for children and adults with allergic rhinitis.
Allergy Extract and dilutions
Allergy Testing

- Nasal smear
- Skin testing
- In vitro testing
Nasal smear

- Looks at nasal secretion component cells
- Can help differentiate allergic rhinitis and NARES (non allergic rhinitis with eosinophilia) from other forms of rhinitis
The goal of testing is to identify antigens to which patients are symptomatically reactive and to quantify the sensitivity if immunotherapy is planned.

There are a variety of acceptable techniques:

- Prick testing, intradermal testing, intradermal dilutional testing, and in vitro testing

Allergy care shall be directed by a trained and competent physician who regularly participates in the care.

Members shall practice in an ethical and fiscally responsible manner.
Screening Tests

- Rapid, efficient, and cost effective method to assess allergy.
- Most allergic individuals will react to common antigens via *in vivo* or *in vitro* techniques.
- Antigens should be representative of what the patient may encounter, and should be geographically based.
Screening Tests

- Negative result usually requires no additional testing
- Positive result requires further testing of other antigens in the group or family. There may be some cross-reactivity, especially with molds.
- Contain 12 to 14 antigens, (pollen, mold, weeds, dust mite, animal dander)
Skin prick/scratch

- Superficial skin reaction, does not penetrate dermis
- Highly specific, sensitive, convenient and safe
- Requires positive (histamine) and negative (saline) control
Skin prick

- Droplet of antigen is introduced about 1 mm deep into the skin.
- Correlates with RAST, and set endpoint dilutional testing (81-89%). Gungor et al Grade A

Disadvantages
- Patient discomfort
- Intertester variability
- Non-standardized allergen extracts, and different interpretation scales
Multitest II
Whealing response
Intradermal testing

- A dilute antigen extract is injected into the dermis, and a superficial wheal forms.
- Causes relatively minimal patient discomfort
- Disadvantages
  - higher risk of anaphylaxis
  - Time intensive
  - Possible false positive
Intradermal dilutional testing

- Intradermal testing utilizing serial dilutions to quantify degree of sensitivity to specific antigen.
- Labor intensive
- Patient discomfort due to multiple sticks
- SET – skin endpoint titration
### SET

- Antigen intradermally introduced
- Wheal size measured after ten minutes.
- Endpoint – 1\textsuperscript{st} dilution that causes positive response (additional growth of wheal > 2mm), followed by confirmatory wheal (growth of at least another 2 mm)
Modified Quantitative Testing

- A hybrid of skin prick and IDT
- Skin prick determines an approximate range of sensitivity, followed by a single intradermal test to further identify the level of sensitivity and quantify the allergic response.
- Corresponds with SET.
In vitro testing

- RAST (radioallergosorbent assay) measures antigen specific IgE
- Safe and highly sensitive
- Better for patients taking beta-blockers (may be impossible to treat anaphylaxis)
- Patients on antihistamines (skin testing is unreliable)
- Patients with dermatographism, and children that cannot tolerate skin testing
RAST

- RAST is a radioimmunoassay test developed in the late 60's for the detection of specific serum IgE antibodies. Initial studies demonstrated a 96% efficiency, sensitivity and specificity.

- The modified RAST is the form now used, introduced by Fadal and Nalebuff in 1977 with the advantages of increased test sensitivity without a loss in specificity.
Modified RAST

- Soluble allergens bound to solid phase support (paper disc) to create a stable immunosorbent media.
- The paper disc is incubated with the test sera, specific IgE antibody will bind to the solid phase allergen.
- The paper disc is then washed to remove all unbound sera and IgE.
- The disc is then exposed to rabbit anti-human IgE antibodies which are radiolabeled. It interacts with the Fc determinant portion on human IgE bound to the solid phase allergen.
- The unbound anti-IgE is washed off the disc and the disc is then quantified by a scintillation counter.
**Modified Rast**

- **Modified RAST scoring system**
- **Class** | **Counts** | **Interpretation**
  - 0 | 250-500 | negative
  - 1/0 | 501-750 | equivocal
  - 1 | 751-1600 | usually positive
  - 2 | 1601-3600 | usually positive with
  - 3 | 3601-8000 | increasing level of specific
  - 4 | 8001-18,000 | IgE
  - 5 | 18,001-40,000
Comparison of tests

- Simons et al performed retrospective chart review of 34 patients undergoing Multi test II and IDT. Grade B
- More antigens positive on IDT
  - Could be more sensitive, or false positive
- Multi test II correlated with IDT endpoint, but may not be clinically significant
IDT positive after negative SPT

- McKay et al (2006) Retrospective chart review of 133 patients undergoing MQT. Grade B
- Patients with < 3mm wheal after SPT, underwent IDT with #2 intradermal (1:500)
- 7 mm wheal considered positive
Findings

- Dust mite demonstrated positive IDT after negative SPT 26.67%
- Cockroach, fulsarium, rough marsh elder, and ragweed had incidences of 16-19%
- Could be secondary to local reaction to glycerin
- Concluded that nasal provocation testing is needed to confirm true allergy or false positive.
IDT vs. SPT vs. MQT

- Peltier et al (2007) performed prospective clinical study with 134 patients testing 5 antigens. Grade A
- 77% concordance rate between results of IDT and MQT.
- Wheal size from SPT is predictive of endpoint IDT.
- MQT nearly as effective as IDT for starting doses for immunotherapy.
Shah et al (2003) performed a direct comparison of Multi testing with SET vs. SET alone. Grade A

50 patients in each group

Found that multi-testing is a cost-effective screening test.

<table>
<thead>
<tr>
<th></th>
<th>Multi-testing</th>
<th>SET testing</th>
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<tbody>
<tr>
<td><strong>Fixed cost</strong></td>
<td>3.82</td>
<td>4.69</td>
</tr>
<tr>
<td><strong>Variable cost</strong></td>
<td>11.95</td>
<td>38.94</td>
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<tr>
<td><strong>Total cost</strong></td>
<td>15.77</td>
<td>43.63</td>
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# Cost (personnel time)

<table>
<thead>
<tr>
<th></th>
<th>Multi- testing</th>
<th>SET</th>
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</thead>
<tbody>
<tr>
<td>Prep (patient)</td>
<td>0.58 min</td>
<td>1.16 min</td>
</tr>
<tr>
<td>Prep (room, equip, supplies)</td>
<td>0.75 min</td>
<td>13.70 min</td>
</tr>
<tr>
<td>Application of test</td>
<td>0.01 min</td>
<td>15.30 min</td>
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<tr>
<td>Record data</td>
<td>0.65 min</td>
<td>10.22 min</td>
</tr>
<tr>
<td>Total time</td>
<td>1.99 min</td>
<td>40.38 min</td>
</tr>
</tbody>
</table>
Cost cont.

- For screening, multi-testing is 1/3 less costly, as well as less time consuming to perform.
- The results from multi-testing can be used to determine the starting point for SET, if immunotherapy is to be employed.
- For quantification, SET can be quite costly and time consuming.
Why perform IDT?

- Seshul (2006) et al. Retrospective chart review of 134 patients undergoing allergy testing. (Grade B)
- Positive skin prick underwent IDT
- Found that SPT correlated poorly to final endpoint concentration.
- IDT is important in finding the strongest starting dose of immunotherapy.
- Starting at highest dose, potentially could shorten the time it takes to reach maintenance dose. Thus, decreasing overall cost of therapy.
## Cost of immunotherapy

<table>
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<tr>
<th></th>
<th>Single shot 1/wk for 52 wks</th>
<th>Vial prep. 4x/yr; 10 U</th>
<th>Length of therapy</th>
<th>Cost</th>
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<tbody>
<tr>
<td>SPT/Intradermal</td>
<td>710.84</td>
<td>352.00</td>
<td>5</td>
<td>5314.20</td>
</tr>
<tr>
<td></td>
<td>710.84</td>
<td>352.00</td>
<td>7</td>
<td>7439.88</td>
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<tr>
<td>SPT/IDT</td>
<td>710.84</td>
<td>352.00</td>
<td>3</td>
<td>3188.52</td>
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</table>
Adjuvant testing

- Nasal endoscopy
- Acoustic rhinometry
- Nasal provocation
Acoustic Rhinometry

- Depends on reflection of acoustic signals from nasal structures
- Provides an image that represents variations in the cross-sectional dimensions of the nasal cavity.
  - Nasal cavity volume, minimal cross-sectional area
  - Does not measure nasal airway resistance
Acoustic Rhinometry
Acoustic rhinometry

- Safe, rapid, and non-invasive
- Can be used on infants, children and adults
- Has been validated by CT and MRI
- Can delineate congestion, from anatomical causes of obstruction
- Uzzamann, A et al. Acoustic rhinometry in the practice of allergy. Ann Allergy, Asthma Immunology. 2006;97:745-752 (Grade D)
Nasal Provocation

- An extension of acoustic rhinometry.
- A metered dose spray of suspected allergen to the nasal cavity
- Must assess response to incremental doses of allergen
- CSA2, corresponds with anterior portion of the inferior turbinate, is most sensitive. (Uzzaman et al)
- Useful for patient’s with workplace allergies. (Dykewicz et al 1998, Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology) Grade A
Future of testing

- Complete testing of allergens, i.e. acoustic rhinometry with nasal provocation, SPT, Intradermal testing, IDT, MQT, and RAST to determine sensitivity/specificity of tests.

- This will help standardize testing for specific allergens.
Key points

- Allergic rhinitis is a type I, IgE mediated, hypersensitivity.
- Environmental and medical management are the mainstays of therapy.
- Immunotherapy is an effective treatment for allergic rhinitis, when medical management fails.
- The goal of testing is to identify antigens to which patients are symptomatically reactive and to quantify the sensitivity if immunotherapy is planned.
Key points

- There are a variety of acceptable techniques:
  - Prick testing, intradermal testing, intradermal dilutional testing, and in vitro testing
- Otolaryngologist need to understand the principles behind SET testing.
Summary

- Allergy testing is an essential part of immunotherapy.
- All tests have strengths and weaknesses.
- The MQT testing utilizes the simplicity of the SPT, and the quantitative accuracy of IDT.
- RAST testing should be used in special circumstances. (unable to tolerate skin prick, beta-blocker therapy, dermatographism).
- More studies are needed to standardize testing for specific allergens.
Bibliography

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