Medical Management of Allergic Rhinitis

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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
Allergic rhinitis

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

- Atopic individuals produce IgE-mast cell TH2 lymphocytic response.
- Low level exposure to antigen, 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 initial damage.
  - Newly formed mediators (leukotrienes and prostaglandins) are produced by breakdown of phospholipid cell membrane.
  - These cause vessels to leak leading to watery rhinorrhea, nasal edema/congestion, and sneezing/pruritus
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.
CD4+ T lymphocyte

- 2 subsets based on distinct cytokines produced
- Th1:
  - produce IL-2, IL-12, interferon (IFN)-gamma
  - activate CD8+ T cell, natural killer cells, and macrophage
  - Elimination of intracellular pathogen, facilitate delayed hypersensitivity
CD4+ T lymphocyte

- **Th2:**
  - produce IL-4, IL-5, IL-10
  - activate B cells and switch antibody synthesis to IgE
  - mediate allergic inflammation
  - preferentially activate Th2 cells leading to development of allergic disease

- Th1 and Th2 inhibit the development of each other
So what do you do with a suspected allergy patient?
History

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

- Rhinorrhea
- Cough/sneezing
- Nasal congestion
- Post nasal drip
- Nasal pruritis
- Watery eyes
- General fatigue
- Diminished quality of life
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 rhinititis**
  - 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**
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
Skin testing guidelines

- Goal 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, 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 multiple 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.

- Disadvantages
  - Patient discomfort
  - Inter-tester 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 intradermaly introduced
- Wheal size measured after ten minutes.
- Endpoint – 1st 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
Medical Management

- nasal steroids
- decongestants
- mast cell stabilizers
- leukotriene receptor antagonists
- anti-IgE globulin

When symptoms persist despite optimal medical management, immunotherapy is an option.
Immunotherapy

- Medical procedure that uses controlled exposure to known allergens to reduce the severity of allergic disease

- Disease accepted to be treated by immunotherapy:
  - Allergic rhinitis, allergic asthma, allergic conjunctivitis, insect sting hypersensitivity

- Disease not accepted to be treated by immunotherapy:
  - Food allergy, urticaria, atopic dermatitis
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
Mechanism: B cell response

- Gradual increase of allergen-specific IgG antibodies -- especially IgG4 subclasses (blocking antibody)
  - intercept and neutralize allergen before it binds to cell-surface IgE
  - form IgG-antigen-IgE complex and bind to the IgG receptor resulting co-aggregation with the IgE receptor and inhibition of IgE receptor triggering
- decreased allergen-specific IgE antibodies
- increase IgA and IgM antigen-specific B lymphocytes
  - May limit antigen penetration into the body from mucosa
Mechanism: T cell response

- Moving immune system from CD4+Th2 cell to Th1 cell pathway
- Alter cytokine production
  - IL-4, IL-5 as Th2 cytokines
  - IFN-gamma as Th1 cytokines
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.
Subcutaneous Immunotherapy

- Only approved route of administration in United States
- Normally involves a weekly subcutaneous injection of an extract of the allergen, in solution, in increasing doses until a standard maintenance dose is reached.
Patient selection

- Proven allergy with skin test or RAST
- With allergic symptoms that are significant to the patient
- Attempts to avoid allergens fail or impractical
- Treatment with medicine is not fully successful or when medication is not well tolerated.
- Young patients without chronic irreversible changes in the upper airways
- Patient needs to be motivated and compliant with treatment
Immunotherapy

- Dose is injected subcutaneously on a regular basis (at intervals of approximately 20 days) for not less than 3 years for perennial allergens.
- **Short term immunotherapy**
  - does not affect the cytokine profile
  - do not have long-term efficacy after discontinuation
- start at an earlier age
  - adverse changes to the immune system can be prevented before they become irreversible
Writing an allergen extract (vaccine) prescription

- Considerations in writing an allergy extract (vaccine) prescription are:
  - decision as to which allergen extracts to include
  - maintenance doses which have been proven to be clinically effective
  - potency of the allergen extracts available
  - patterns of cross-reactivity and
  - deleterious effects of some allergen extracts on others with which they may be mixed.
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.
Allergy Extract and dilutions
Allergens

- Extracts of some allergens have been shown to contain proteases capable of degrading the proteins in other extracts with which they may be mixed.
- Proteases have been reported in fungal and whole body insect extracts.
- Best general rule is to not mix cockroach or fungal extracts with pollen, mite, or dander extracts.
Effective target doses of the standardized extracts have been defined in terms of their major allergen content.

Method of standardization employed in US (bioequivalent allergen units and major allergen content in FDA units) does not allow use of this information on dosing.

However, representative lots of standardized extracts have been assessed for their major allergen content:
- Allows an approximation of proven doses,
- But range of major allergen content for extracts labeled with the same US standardized potency is quite broad.
Standardized Extracts

- In many cases the allergen extract manufacturer is able to provide major allergen potency for a particular lot of their extract.

- Unstandardized extracts can only be dosed based on analogy to standardized extracts or by what is known or suspected to be their potency.
### Major allergen content of US standardized extract

<table>
<thead>
<tr>
<th>Allergen extract (number of extracts tested)</th>
<th>Expressed potency</th>
<th>Major allergen</th>
<th>Mean content of major allergen</th>
<th>Minimum content of major allergen</th>
<th>Maximum content of major allergen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kentucky blue grass (n = 23)</td>
<td>100 000 BAU/mL</td>
<td>Poa p 5</td>
<td>300 μg/mL</td>
<td>118 μg/mL</td>
<td>482 μg/mL</td>
</tr>
<tr>
<td>Timothy (n = 28)</td>
<td>100 000 BAU/mL</td>
<td>Phl p 5</td>
<td>680 μg/mL</td>
<td>354 μg/mL</td>
<td>1336 μg/mL</td>
</tr>
<tr>
<td>Bermuda grass</td>
<td>10 000 BAU/mL</td>
<td>Cyn d 1</td>
<td>300 μg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ragweed (n = 21)</td>
<td>1:10 w/v</td>
<td>Amb a 1</td>
<td>424 μg/mL</td>
<td>114 μg/mL</td>
<td>763 μg/mL</td>
</tr>
<tr>
<td><em>D. pteronyssinus</em> (n = 38)</td>
<td>10 000 AU/mL</td>
<td>Der p 1</td>
<td>76 μg/mL</td>
<td>19 μg/mL</td>
<td>241 μg/mL</td>
</tr>
<tr>
<td><em>D. pteronyssinus</em> (n = 38)</td>
<td>10 000 AU/mL</td>
<td>Der p 2</td>
<td>69 μg/mL</td>
<td>12 μg/mL</td>
<td>153 μg/mL</td>
</tr>
<tr>
<td><em>D. farinae</em> (n = 59)</td>
<td>10 000 AU/mL</td>
<td>Der f 1</td>
<td>56 μg/mL</td>
<td>14 μg/mL</td>
<td>144 μg/mL</td>
</tr>
<tr>
<td><em>D. farinae</em> (n = 59)</td>
<td>10 000 AU/mL</td>
<td>Der f 2</td>
<td>72 μg/mL</td>
<td>4 μg/mL</td>
<td>182 μg/mL</td>
</tr>
<tr>
<td>Cat hair/epithelium (n = 45)</td>
<td>10 000 BAU/mL</td>
<td>Fel d 1</td>
<td>43 μg/mL</td>
<td>24 μg/mL</td>
<td>79 μg/mL</td>
</tr>
<tr>
<td>Dog hair</td>
<td>1:10 w/v</td>
<td>Can f 1</td>
<td>5.4 μg/mL</td>
<td>0.5 μg/mL</td>
<td>7.2 μg/mL</td>
</tr>
<tr>
<td>AP dog</td>
<td>1:100</td>
<td>Can f 1</td>
<td>140 μg/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Extracts

- Unstandardized pollen extracts
  - assumed to approximate standardized grasses and ragweed in potency,
  - cockroach extracts have been shown to be quite weak.
- Major allergen content of a number of commercial fungal extracts have been shown to be low and very variable among different manufacturers.
Starting Concentration

- Clinical experience indicates that the 1:1000 v/v dilution of the maintenance vial is generally a safe starting concentration.
- Skin endpoint titration can also be used to determine starting dose, based on dilution which elicited positive reaction.
- Patients may also be prick skin tested with each dilution of extract mix and immunotherapy commenced with the most dilute concentration that yields a positive prick skin test.
## Allergen immunotherapy prescription form

<table>
<thead>
<tr>
<th>Allergen extract</th>
<th>Target dose of major allergen</th>
<th>Amount of major allergen required in 10 mL</th>
<th>Mean concentration of major allergen in 1 mL of stock extract</th>
<th>Amount of stock extract to be added to 10 mL vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short ragweed</td>
<td>12.0 μg Amb a 1</td>
<td>240 μg</td>
<td>424 μg/mL of 1:10 w/v</td>
<td>0.6 mL 1:10 w/v</td>
</tr>
<tr>
<td>Timothy</td>
<td>20 μg Phl p 5</td>
<td>400 μg</td>
<td>680 μg/mL of 100 000 BAU</td>
<td>0.6 mL 100 000 BAU/mL</td>
</tr>
<tr>
<td><em>D. pteronyssinus</em></td>
<td>7.0 μg Der p 1</td>
<td>140 μg</td>
<td>76 μg/mL of 10 000 AU</td>
<td>1.8 mL 10 000 AU/mL</td>
</tr>
<tr>
<td>Cat</td>
<td>15 μg Fel d 1</td>
<td>300 μg</td>
<td>43 μg/mL of 10 000 AU</td>
<td>7.0 mL 10 000 AU/mL</td>
</tr>
</tbody>
</table>
CONVENTIONAL ALLERGEN EXTRACT TREATMENT SCHEDULE

- Begin with *Vial # 5* and progress to *Vial #1*, which is the most concentrated or 'maintenance' solution.
- The injections should be given every *week*.
- Once maintenance is reached, the injection should be given every 3 to 4 weeks with the following exceptions:
  - *give weekly for first month and*
  - *every two weeks for the second month.*

<table>
<thead>
<tr>
<th>Vial #5</th>
<th>Vial #4</th>
<th>Vial #3</th>
<th>Vial #2</th>
<th>Vial #1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 mL</td>
<td>0.05 mL</td>
<td>0.05 mL</td>
<td>0.05 mL</td>
<td>0.05 mL</td>
</tr>
<tr>
<td>0.10 mL</td>
<td>0.10 mL</td>
<td>0.10 mL</td>
<td>0.07 mL</td>
<td>0.07 mL</td>
</tr>
<tr>
<td>0.20 mL</td>
<td>0.20 mL</td>
<td>0.20 mL</td>
<td>0.10 mL</td>
<td>0.10 mL</td>
</tr>
<tr>
<td>0.40 mL</td>
<td>0.40 mL</td>
<td>0.40 mL</td>
<td>0.15 mL</td>
<td>0.15 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.25 mL</td>
<td>0.20 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.35 mL</td>
<td>0.30 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.50 mL</td>
<td>0.40 mL</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.50 mL</td>
</tr>
</tbody>
</table>
Advantage of immunotherapy

- may prevent progression of rhinitis to asthma in children
- Preventive Allergy Treatment Study:
  - 205 children from 6 pediatric allergy centers in northern Europe aged 6-14 years with grass or birch pollen allergy
  - randomly assigned either to receive specific immunotherapy for 3 years or to a control group
  - The children who were treated with immunotherapy had significantly fewer asthma symptoms after 3 years as evaluated by clinical diagnosis
- may prevent onset of new sensitization in allergic patients
Immunotherapy with Omalizumab

- Double blind placebo-controlled study of ragweed immunotherapy
- Observed that SCIT alone induced allergen-specific IgG4 that partially blocked binding of allergen-IgE complexes to cells
- This binding was completely blocked with the addition of omalizumab

Modified Extracts

- Recombinant allergens can be modified for immunotherapy.
  - deletion or site-directed mutagenesis
    - IgE epitopes can be removed from recombinant allergens without affecting the ability of the molecules to interact with T cells

- Result is a decrease in allergenicity without reducing immunogenicity.
Sublingual immunotherapy

- widely used and investigated in Europe since late 1980’s
- keep the extract under the tongue for a couple of minutes and then swallow it
- dose of allergen is greater than subcutaneous immunotherapy (about 3-300 times higher)
Efficacy of sublingual immunotherapy

- Wilson et al. (2005)
  - systemic review of literature in Cochrane library
  - 22 clinical studies, a total of 979 patients
  - double-blinded, placebo-controlled, parallel-group studies
  - highly significant reduction in symptoms as well as definite decrease in medicine intake for symptoms
  - whether sublingual therapy equals the efficacy of subcutaneous immunotherapy is not clear
Sublingual therapy Dosing Study

- Multinational, randomized, double-blind, placebo-controlled study
- 628 adults with grass pollen-induced rhino-conjunctivitis were assigned to either different concentrations of sublingual therapy (100, 300, 500 IR)
- Concluded that the 300 IR grass pollen tablet was the optimal dose for treatment

Conclusions

- Immunotherapy is a viable option for pts not benefiting from medical management
  - works by altering one’s immunologic response
- Adjuvant therapies may be useful to maximize effect of immunotherapy