Nonallergic Rhinitis Evaluation and Treatment

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Nonallergic Rhinitis

- A Diagnosis of Exclusion
- Candidates have
  ✓ Negative allergy skin tests or RAST tests
  ✓ No infectious process
- No definitive diagnostic test
- Diagnosis based primarily on clinical features and associated conditions

Overlap in Common Causes of Rhinitis

Three major types of chronic rhinitis

- Allergic Rhinitis
- Non Allergic Rhinitis
- Infection (Sinusitis)

Nonallergic Rhinitis

- Little prevalence data for nonallergic rhinitis syndromes
- 52% of patients seen in an allergy clinic were found to have nonallergic rhinitis
- Female>male in a few studies looking at epidemiology

Overlap in Non-Infectious Causes of Rhinitis

Combined Nonallergic 57%

Pure Allergic 43%

Allergic Rhinitis

Mixed 34%

Pure Nonallergic 23%

Non Allergic Rhinitis

Rhinitis

Allergic

Sneezing
Itch
Eye symptoms
Pressure
Headache
Posterior Rhinorrhea
Congestion

Nonallergic

Sneezing
Itch
Eye symptoms
Pressure
Headache
Posterior Rhinorrhea
Congestion

Mechanistic Classification: Nonallergic Noninfectious Rhinitis

- Inflammatory
  - Eosinophils
    - NARES/BENARES
    - Polyps
  - Neutrophils or Mixed
    - Vasculitis/Autoimmune

- Non Inflammatory (No Leukocytes)
  - Eosinophil
  - Neutrophil
  - Mixed
  - Epithelial Dysplasia
  - Neural
  - Hormonal
  - Structural
  - Atrophic
  - Vasculitis
  - Sympathetic
  - Pregnancy
  - Neociceptive
  - Thyroid
  - Tumors
  - Sympathetic
  - Parasympathetic
  - Pregnancy
  - Trauma
  - Maximal disruption
  - Offactory
  - Anatomic/ Trauma
  - Occupational
### Mechanistic Classification: Nonallergic Noninfectious Rhinitis

- **Non-Inflammatory**
  - Drug Induced
  - Epithelial dysfunction
  - Occupational/Irritant
  - Hormonal
  - Structural
  - Idiopathic/Neural/Vasomotor

### Nonallergic Rhinitis with Eosinophilia Syndrome (NARES)

- Good response to intranasal corticosteroids. Budesonide, beclomethasone and fluticasone have indications for nonallergic rhinitis.
- Oral antihistamines some efficacy in only a few studies.
- Subtypes of the condition with blood eosinophilia (BENARES)
- Patients sometimes describe antigen triggers

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### Nonallergic Rhinitis with Eosinophilia Syndrome (NARES)

- Perennial symptoms similar to allergic rhinitis
  - Sneezing, rhinorrhea, nasal itch, congestion, anosmia
- Eosinophilia on nasal smears
- Negative allergy skin tests or RAST tests
- Associated with asthma, aspirin intolerance and nasal polyps

### Positive nasal allergen challenges in patients with persistent nonallergic rhinitis

Evidence for localized allergic response

- 54% of persistent nonallergic rhinitis patients (PNAR) showed positive nasal allergen provocation tests (NAPT) to *D. pteronyssinus* (DP) dust mite
- 22% had nasal specific IgE to DP mite in the face of negative skin tests and serum specific IgE to DP

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Nasal Polyps

Benign polypoid masses arising from inflamed nasal mucosa.

Contain eosinophils, lymphocytes, plasma cells and mucin with few nerves.

Nasal Polyps

- Pathophysiology unknown
- Recurrent infections contribute
- Increased histamine, leukotrienes and serotonin
- Not IgE-mediated
- Respond to corticosteroids
- Possible role for leukotriene inhibitors

Nasal Polyps

Associated with
- Aspirin intolerance
- Sampter's syndrome
  ✓ aspirin intolerance, asthma, nasal polyps, sinusitis.
- Cystic Fibrosis
- Churg-Strauss syndrome
- Chronic sinusitis
- Ciliary dyskinesia
- Young syndrome
- Allergic fungal sinusitis

Systemic Autoimmunity/Vasculitis

- Churg-Strauss syndrome
- Systemic lupus granulomatosis
- Wegener’s granulomatosis
### Systemic Autoimmunity/Vasculitis

- Sarcoidosis
  - Treat underlying condition
  - Topical corticosteroids
- Sjogren’s syndrome
  - Treatment of xerostomia with nasal saline sprays, moisturizing nasal gels, sialagogues

### Drug Induced Nonallergic Rhinitis

- Rhinitis Medicamentosa
  - Topical decongestants
- Oral Contraceptives/Hormone Replacement Therapy
- Psychotropic agents

### Drug Induced Nonallergic Rhinitis

- Non-Steroidal Anti-Inflammatory Drugs
  - (NSAID Rhinitis, ASA Triad)
- Antihypertensives
  - ACE Inhibitors
  - Hydralazine
  - Beta-blockers

### Epithelial Dysfunction

#### Atrophic Rhinitis

1. Epistaxis, nasal crusting, stuffiness, halitosis
   1. Excessive surgical removal of nasal mucosa
   1. Treatment with nasal saline rinses and moisturizing agents
2. Klebsiella infection in elderly
   1. Treatment with antibiotics
<table>
<thead>
<tr>
<th>Epithelial Dysfunction</th>
<th>Occupational/Irritant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2) Profuse rhinorrhea in elderly</td>
<td>✓ Corrosive effects with epithelial injury</td>
</tr>
<tr>
<td>1) Possible parasympathetic overactivity</td>
<td>✓ Irritant Rhinitis</td>
</tr>
<tr>
<td></td>
<td>• Smoke, paint, air pollution, dust</td>
</tr>
<tr>
<td>1) Treatment with intranasal ipratropium bromide</td>
<td>✓ Physical Stimuli</td>
</tr>
<tr>
<td></td>
<td>• Cold dry air, bright lights</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupational/Irritant</th>
<th>Hormone Induced Nonallergic Rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Many causative agents in the workplace or home</td>
<td>• Rhinitis of Pregnancy</td>
</tr>
<tr>
<td>✓ Can be inflammatory or non-inflammatory</td>
<td>• Hormone replacement therapy and oral contraceptive associated rhinitis</td>
</tr>
<tr>
<td>✓ Immunologic responses</td>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td>• Comparable to agents of occupational lung disease</td>
<td>• Acromegaly</td>
</tr>
</tbody>
</table>
Structural Rhinitis

- Septal deviation or other obstructing abnormality can aggravate rhinitis
- Tumors
- Cerebral Spinal fluid leak
  - Associated with trauma or surgery
  - CSF contains glucose and β₂-transferrin

Idiopathic Rhinitis

- Exclusion criteria
  - Positive allergy test
  - Smoking
  - Nasal polyps
  - Anatomical abnormality
  - Infection
  - Pregnancy, lactation, hormone replacement
  - Medications affecting nasal function
  - Beneficial effect of nasal corticosteroid (NARES)


Idiopathic Rhinitis

- Is the new vasomotor rhinitis
- Corresponds to “neural” or “reflex” rhinitis
- “After having excluded all known causes of chronic rhinitis……”
- Nasal hyperreactivity key feature


Idiopathic Rhinitis

- Selection criterion
  - Nasal hyperreactivity
    - To nonspecific stimuli
      - Smoke, spices, strong odors, and other irritants
### Idiopathic Rhinitis

**Importance of neurologic vascular control**
- Hyperactive parasympathetic system
- Hypoactive sympathetic system
- Overactivity of C-fibers of the nonadrenergic noncholinergic system

- Enhanced release of substance p and other neuropeptides

### Summary: Treatment of Nonallergic Rhinitis

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eliminate triggers and treat identifiable causes</strong></td>
<td><strong>Pruritis</strong></td>
</tr>
<tr>
<td>Nasal corticosteroid</td>
<td>Sneezing</td>
</tr>
<tr>
<td>Add Ipratropium</td>
<td>Congestion</td>
</tr>
<tr>
<td>Antihistamine Oral or Azelastine</td>
<td>Rhinorrhea</td>
</tr>
<tr>
<td>(Leukotriene inhibitors Proposed)</td>
<td></td>
</tr>
<tr>
<td>Azelastine</td>
<td>With or without nasal saline rinses</td>
</tr>
</tbody>
</table>

### Efficacy of topical antihistamine in idiopathic rhinitis

Azelastine effective for the treatment of Idiopathic (vasomotor) rhinitis in two DBPC trials.

### Allergic Rhinitis: Initial Diagnosis and Treatment

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Nationwide Children’s Hospital

<table>
<thead>
<tr>
<th><strong>Chief Complaint</strong></th>
<th><strong>Age Matters</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sneezing</td>
<td>• Adolescents and Adults</td>
</tr>
<tr>
<td>• Runny Nose</td>
<td>✓ Allergic Rhinitis</td>
</tr>
<tr>
<td>• Nasal Congestion</td>
<td>✓ Non-Allergic Rhinitis/Vasomotor Rhinitis</td>
</tr>
<tr>
<td>• Facial Pressure</td>
<td>✓ Infection (viral URI or sinusitis)</td>
</tr>
<tr>
<td>• Headache</td>
<td>✓ Obstructing polyps, septal deviation</td>
</tr>
<tr>
<td>• Facial Pain</td>
<td></td>
</tr>
<tr>
<td>• Ear Pressure/fullness</td>
<td></td>
</tr>
<tr>
<td>• Eyes water or itch</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Chief Complaint</strong></th>
<th><strong>Age Matters</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased Smell</td>
<td>• Children</td>
</tr>
<tr>
<td>• Decreased Taste</td>
<td>✓ Infection</td>
</tr>
<tr>
<td>• Bad Breath</td>
<td>✓ Allergic Rhinitis (generally &gt;2 y/o)</td>
</tr>
<tr>
<td>• Cough</td>
<td>✓ Non-Allergic Rhinitis/Vasomotor Rhinitis</td>
</tr>
<tr>
<td>• Sore Throat</td>
<td>– Irritant (esp. tobacco smoke)</td>
</tr>
<tr>
<td>• Throat Clearing</td>
<td>✓ Obstruction (Adenoid hypertrophy, foreign body)</td>
</tr>
<tr>
<td>• Throat Drainage</td>
<td></td>
</tr>
<tr>
<td>• Sinus Infections</td>
<td></td>
</tr>
</tbody>
</table>
Exam Pearls

- Edema and venous sinusoid congestion leads to swollen pale or blue turbinates
- Clear middle ear fluid is common with significant congestion
- The eyes are important (redness, swelling, shiners, Dennie’s lines)
- Other sign of atopy—asthma, eczema

Skin Testing

- History dictates what antigens are to be tested
- Interpreted only in the context of the clinical history

Skin Testing

- Testing should be to relevant local antigens
- Pollen seasons and indoor allergen patterns help interpret history
  - Spring-Trees; Summer-Grass; Fall-Weeds

Population Data

<table>
<thead>
<tr>
<th>Allergens tested</th>
<th>Percentage (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor allergens</td>
<td></td>
</tr>
<tr>
<td>Dust mite</td>
<td>27.5 (0.82)</td>
</tr>
<tr>
<td>German cockroach</td>
<td>26.1 (0.85)</td>
</tr>
<tr>
<td>Cat</td>
<td>17.9 (0.89)</td>
</tr>
<tr>
<td>At least one indoor allergen</td>
<td>43.0 (1.57)</td>
</tr>
<tr>
<td>Outdoor allergens</td>
<td></td>
</tr>
<tr>
<td>Personal =</td>
<td>26.0 (0.84)</td>
</tr>
<tr>
<td>Animal =</td>
<td>26.2 (0.83)</td>
</tr>
<tr>
<td>Bermuda grass =</td>
<td>18.2 (0.94)</td>
</tr>
<tr>
<td>Bee venom =</td>
<td>15.2 (0.92)</td>
</tr>
<tr>
<td>White oak =</td>
<td>15.2 (0.79)</td>
</tr>
<tr>
<td>Alexander alternata</td>
<td>12.2 (0.99)</td>
</tr>
<tr>
<td>At least one outdoor allergen</td>
<td>46.0 (1.25)</td>
</tr>
<tr>
<td>Food allergies =</td>
<td></td>
</tr>
<tr>
<td>Peanut =</td>
<td>8.0 (0.84)</td>
</tr>
<tr>
<td>At least one indoor or outdoor allergen</td>
<td>53.9 (0.82)</td>
</tr>
<tr>
<td>At least one of any type</td>
<td>54.3 (0.80)</td>
</tr>
</tbody>
</table>

**RAST Testing**

- A number describing the amount of allergen specific IgE
- Should be interpreted in context of total IgE, symptoms
- No defined level for each antigen to predict clinical symptoms

**Test Performance-Cat Allergy**

**TABLE 8: Predictive value of skin tests and RASTs**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAST</td>
<td>87.2 (±6.9)</td>
<td>91.1 (±5.9)</td>
<td>96.4 (±6.4)</td>
<td>90.1 (±5.3)</td>
<td>88.6 (±5.4)</td>
</tr>
<tr>
<td>LEUK</td>
<td>93.6 (±4.3)</td>
<td>80.1 (±7.5)</td>
<td>90.1 (±5.3)</td>
<td>87.1 (±6.0)</td>
<td>88.2 (±5.4)</td>
</tr>
<tr>
<td>LEAP</td>
<td>86.0 (±3.8)</td>
<td>80.5 (±6.6)</td>
<td>76.3 (±5.9)</td>
<td>97.0 (±3.5)</td>
<td>87.5 (±7.2)</td>
</tr>
<tr>
<td>PLC</td>
<td>79.2 (±3.9)</td>
<td>90.6 (±4.4)</td>
<td>82.5 (±5.7)</td>
<td>74.3 (±0.6)</td>
<td>80.4 (±0.2)</td>
</tr>
<tr>
<td>BING</td>
<td>80.0 (±5.3)</td>
<td>81.0 (±0.7)</td>
<td>83.0 (±0.7)</td>
<td>81.0 (±0.5)</td>
<td>81.0 (±0.5)</td>
</tr>
</tbody>
</table>

**J Allergy Clin Immunol 1999;103:773-9.**

**ARIA Classification**

- **Intermittent**
  - Less than 4 days/week OR
  - less than 4 weeks/year

- **Persistent**
  - More than 4 days/week AND
  - more than 4 weeks/year

- **Mild**
  - No Sleep Disturbance
  - No Impairment of school, work or desired activities
  - No “Troublesome” symptoms

- **Moderate-Severe**
  - Sleep Disturbance
  - Impairment of school, work or desired activities
  - “Troublesome” symptoms

**Bousquet J. El al. JACI 2001; 108(suppl) S147-334.**
Treat the early and late phase symptoms.

**Stepwise treatment---Allergic**

- **Step 1:** Antihistamine or Nasal Corticosteroid

**Stepwise treatment---Allergic**

- **Step 1:** Antihistamine or Nasal Corticosteroid
  - **Step 2:** Nasal Corticosteroid AND Antihistamine or Leukotriene modifier
Stepwise treatment—Allergic

Step 1: Antihistamine or Nasal Corticosteroid

Step 2: Nasal Corticosteroid AND Antihistamine or Leukotriene modifier

Step 3: Nasal Steroid/Antihistamine/Leukotriene modifier

Allergen Immunotherapy

Referral for testing at any stage

Treat the Symptoms

- Primarily — Itch, Sneeze, Rhinorrhea
  - Antihistamine (oral or intranasal)
  - Weekend symptoms
Treat the Symptoms

- Primarily Congestion
  - First line should be nasal corticosteroid
  - Leukotriene modifier
  - Decongestant

Indications for Immunotherapy

- Failure of medical treatment
- Desire to decrease long term medication use
- Intolerance to medication of side effects
- Allergic rhinitis and asthma (or possible prevention of asthma)
- Venom anaphylaxis

Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy

<table>
<thead>
<tr>
<th>Pollen Count</th>
<th>Initial Placebo Trial</th>
<th>Current Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Score</td>
<td>Pollen Count</td>
<td>Symptom Score</td>
</tr>
</tbody>
</table>


SLIT

- Sublingual Immunotherapy—a future alternative to subcutaneous IT
- Multiple dosing forms exist (extract, tablet)
- Increased safety profile
- Can be done at home
- Dose varies by antigen, not established yet for US extracts
**SLIT**

- Currently undergoing clinic trials in the US
- Similar immunologic changes to Subcutaneous immunotherapy
- Increased $T_{reg}$ cells
- Blunted seasonal rise in IgE, increased antigen specific IgG$_4$

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**ISS Conjugated Proteins**

- Amb a 1-ISS has shown benefit in ragweed allergic patients
- Administered as six escalating doses before 2001 pollen season
- Followed for 2001 and 2002

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**ISS Conjugated Proteins**

- ISS is unmethylated CpG DNA, a strong immune stimulus
- Stimulate TLR-9
- Published use in ragweed allergy

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**Ragweed Results**

Creticos, PS et al. NEJM 2006;355:1445-1455

Creticos, PS et al. NEJM 2006;355:1445-1455
**Allergic Rhinitis--Summary**

- Treat the patient’s symptoms and pick the treatment to fit the symptoms
- Discover and remove triggers
- Diagnosis—History/Exam will exclude likely causes
- Re-evaluate if symptoms don’t respond
- Patients often have multiple causes

**Treatment Summary**

- Often a combination of medication is necessary—stepwise approach to treatment aids decision making
- Immunotherapy has multiple indications
- Multiple new administration methods and preparations in future