Allergic Rhinitis | Epidemiology

- Leading cause of chronic illness
- Over 50 million Americans suffer from allergies
- 10-30% of children and adults affected in the U.S.
- 2.5% of all clinician visits

Allergic Rhinitis | Economic Burden

- Lost school days per year: 2 million
- Lost work days: 6 million
- Avg # of annual prescriptions vs patients with AR: 2x
- Direct annual cost: > $2-5 billion
- Indirect annual cost: > $2-4 billion

AR causes greater loss of productivity than any other illness and accounts for ~1/4 of all lost productivity.

Allergic Rhinitis | Quality of Life

- Sleep disturbed breathing
  - Caused by congestion
  - Hundreds of brief and subtle “microarousals” each night

- Cognitive and psychiatric issues in children and adolescents
  - Attention-deficit hyperactivity disorder
  - Lower exam scores during peak pollen seasons
  - Poor concentration
  - Impaired athletic performance
  - Low self-esteem

- Cognitive and psychiatric issues in adults
  - Anxiety & depression
  - Reduced academic performance and work productivity
  - Impaired sexual performance

What is Allergic Rhinitis (AR)?

- Inflammatory, IgE-mediated disease characterized by nasal congestion, rhinorrhea (nasal drainage), sneezing, and/or nasal itching

- Inflammation of the inside lining of the nose that occurs when a person is sensitized
  - Animal dander
  - Pollen
  - House dust mites

Allergic Rhinitis | Pathophysiology

Early-phase Reaction (Max at 10-30 Minutes)
- Allergens
- IgE antibodies
- Mediator release
- Blood vessels
- Nasal glands
- Sneezing
- Rhinorrhea
- Congestion

Late-phase Reaction (Max at 10-12 Hours)
-Late phase reaction
-Hypersensitivity
-Resolution
-Complications
-Inreversible disease (?)

Allergic Rhinitis Diagnosis
Questions To Ask a Patient With AR

- Do you have nasal congestion, runniness and/or sneezing?
- Do you have itchy, red and/or watery eyes?
- Are your symptoms impacting your daily activities or sleep?
- Do your symptoms change over the year and are they seasonal?
- Have antihistamines and/or prescription nasal sprays been effective? Have they been used consistently and had an adequate trial?

Allergic Rhinitis | **Risk Factors**
- Family history of atopy
- Male sex
- Birth during the pollen season
- Firstborn status
- Early use of antibiotics
- Maternal smoking exposure in the first year of life
- Exposure to indoor allergens, such as dust mite allergen
- Serum IgE >100 int. units/mL before age six
- Presence of allergen-specific immunoglobulin E (IgE)

Presence of each of these factors was associated with a 3-5 positive likelihood ratio for the diagnosis of allergic rhinitis.

Allergic Rhinitis | **Differential Diagnosis**

**Non-allergic Rhinitis syndromes**
- Vasomotor rhinitis (idiopathic rhinitis)
- Drug-induced rhinitis (e.g., ACE inhibitors, PDE-5 inhibitors, α-antagonists, NSAIDs, oral contraceptives)
- Rhinitis medicamentosa due to topical decongestants or cocaine
- Infectious rhinitis
- Hormonal rhinitis
- Pregnancy rhinitis - reported in 20%-30% of pregnancies

**Differential Diagnosis**
- Nasal polyps
- Nasal septal deviation
- Tumors
- Hypertrophy of the nasal turbinates
- Cleft palate
- Laryngopharyngeal reflux
- Foreign body obstruction

**Other causes of disturbed olfactory function**
- Cystic fibrosis
- Primary ciliary dyskinesia or other ciliary dysfunction
- Sinus disease
- Vasculitis (such as granulomatosis with polyangiitis)
- Cerebrospinal fluid rhinorrhea

Allergic Rhinitis | **IgE-specific Tests**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Recommendation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin tests (Skin prick or intradermal)</td>
<td>Recommend</td>
<td>Allows for direct observation of the body's reaction to a specific antigen</td>
<td>Possible systemic allergic reaction (anaphylaxis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered more sensitive than blood testing</td>
<td>May be affected by patient medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intradermal can be used when additional sensitivity is required or skin prick negative</td>
<td>Less expensive than blood testing</td>
</tr>
<tr>
<td>Blood</td>
<td>Recommend</td>
<td>No risk of anaphylaxis</td>
<td>Requires reliable laboratory potential for laboratory errors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be used for patients with skin conditions such as dermatomycosis or severe eczema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be used for patients on β-blockers or with comorbid medical conditions that preclude skin testing</td>
<td></td>
</tr>
<tr>
<td>IgE or total IgE</td>
<td>Recommend against</td>
<td>Does not yield information helpful for management of AR</td>
<td></td>
</tr>
</tbody>
</table>

Allergic Rhinitis | **Classification**

- **Seasonal AR**
- Can be diagnosed by history alone if there is an obvious connection between exposure and the onset of symptoms (e.g., exposure to animals)
- **Episodic AR**
- **Perennial AR**

<table>
<thead>
<tr>
<th>Seasonal AR</th>
<th>Episodic AR</th>
<th>Perennial AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>1-4 days per week</td>
<td>4 weeks per year</td>
</tr>
<tr>
<td>Persistent</td>
<td>1-4 days per week</td>
<td>4 weeks per year</td>
</tr>
</tbody>
</table>

2. 1. Wallace DV, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2008 Aug;122(2 Suppl):S1-84
Allergic Rhinitis | Diagnostic Approach

**Characteristic symptoms**
- Paroxysms of sneezing, rhinorrhea, nasal obstruction, nasal itching, postnasal drip, cough, irritability, and fatigue

**Suggestive Clinical History**
- i.e. Presence of risk factors

**Physical Exam**
- “Allergic shiners”, Dennie-Morgan lines, “Allergic salute”, and “Allergic facies”

**Imaging**
- NOT usually performed unless a concomitant condition (i.e. chronic rhinosinusitis)

**Sensitization testing**
- Indicated when symptoms prove difficult to manage or the trigger(s) for the symptoms are not apparent

Allergic Rhinitis Treatment

**Environmental control measures and allergen avoidance**

**Pharmacological management**

**Allergen immunotherapy**

**Treatment | Allergen Avoidance**

**Pollens & outdoor molds**
- Reduction of outdoor exposure during the season
- Limit outdoor exposure on dry, sunny, and windy days
- Keep windows and doors of the house/car closed as much as possible
- Shower after outdoor exposure

**Indoor allergens**
- Humidifier (<50% humidity)
- Removal of standing water
- Removal of pets
- Dust barriers for pillows and mattresses
- HVAC and free-standing air filters
- HEPA vacuum cleaners

**Treatment | Pharmacotherapy**

**Intermittent: Mild-Moderate**
- Environmental Control AND Non-sedating 2nd generation oral antihistamines (AH, PRN)

**Persistent: Mild**
- Environmental Control AND AH and/or INCS or INAH
- Specialist referral

**Persistent: Moderate**
- Environmental Control AND AH + INCS or INAH
- Specialist referral

**Severe**
- Environmental Control AND AH + INCS + INAH
- Consider PO steroid (5d)
- Specialist referral

AHs = Loratadine, desloratadine, cetirizine, fexofenadine, and levocetirizine
INCS = Triamcinolone, mometasone furoate, fluticasone, and budesonide
INAH = Azelastine, olopatadine, azelastine/fluticasone


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INAH = Azelastine, olopatadine, azelastine/fluticasone

Allergic Rhinitis | Treatment

Environmental control measures and allergen avoidance

Pharmacological management

Allergen immunotherapy

Case 1 | David

25-year-old male student

- Chief Complaint: Allergic symptoms despite treatment
- PMHs: Asthma
- Current Treatment: Environmental control, INAH, and INC
- Allergen Testing: polensensitization to trees, grass, cat, and dogs (usually worse in the spring)

- Is further testing indicated?
- What are his treatment options at this time?
- When would you refer this patient?
Approach to Allergic Rhinitis

- History should suggest AR
- Look for associated issues such as atopic dermatitis, asthma, family history
- Consider trial of non-sedating antihistamines, intranasal corticosteroids
- Specific allergen-avoidance suggestions should be based on proper allergy-testing results
- Pharmacotherapy
- Immunotherapy
- Consider referral to Allergy/Immunology

Treatment | Overview of Allergen Immunotherapy (AIT)

- One-third of children and two-thirds of adults with AR experience insufficient relief with pharmacotherapy alone
- AIT involves controlled, repetitive dosing of allergen(s) in patients diagnosed with AR by history and specific IgE allergy testing
- AIT is the only potential curative therapy for SAR and/or PAR
- AIT should be considered in patients uncontrolled by allergen avoidance, regular use of medications, and those wishing to increase immune tolerance to the allergen(s)
- Important considerations in initiating AIT include patient preference, acceptance, expected adherence, and costs

<table>
<thead>
<tr>
<th>SCIT</th>
<th>SLIT-T</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness for AR</strong></td>
<td>Supported by systematic reviews of RCTs</td>
</tr>
<tr>
<td>Safety</td>
<td>Deaths: 1 per 2.5 million injections</td>
</tr>
<tr>
<td>Rate of systemic reactions</td>
<td>0.50%-6.8%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Administered in clinician’s office</td>
</tr>
<tr>
<td>FDA status</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Socioeconomic</td>
<td>CPT code exists for SCIT allergen preparation and injections</td>
</tr>
</tbody>
</table>

SCIT | Dosing Regimen

**Up-dosing Phase**
- Individual titration
- Increasing doses are administered to:
  - Safely build up to a maintenance dose
  - Carefully assess the sensitivity of the patient

**Maintenance Phase**
- Practice parameters recommended maximal dose given every 2-4 weeks for 3-5 years

SCIT | Efficacy

**Systematic Review (74 RCTs)**
Compared to control in patients with rhinitis & rhinoconjunctivitis, SCIT was associated with:

- High-strength evidence for improvement in:
  - Rhinitis/rhinoconjunctivitis symptoms (based on 26 trials with 1,704 patients)
  - Conjunctivitis symptoms (based on 14 trials with 1,104 patients)
  - Combined nasal plus ocular plus bronchial symptoms (based on 6 trials with 591 patients)
  - Combined rhinitis/rhinoconjunctivitis plus asthma medication use (based on 11 trials plus 768 patients)
  - Rhinoconjunctivitis disease-specific quality of life (based on 6 trials with 425 patients)

- Moderate-strength evidence for improvement in:
  - Rhinitis/rhinoconjunctivitis disease-specific quality of life (based on 25 trials and 704 patients)

- Low-strength evidence for improvement in:
  - Combined rhinitis/rhinoconjunctivitis with or without asthma symptom and medication scores (based on 6 trials with 400 patients)

**Case 1 | David**

**Build-up regimen**
- Tolerated well

**Maintenance therapy (months)**
- Experienced more symptom-free days

**Subsequent visits**
- Decrease in rescue medications
- Eventual removal of controller therapies

**Longitudinal follow-up**
- Confirmed long-lasting relief
SLIT-T | Overview of Trials

Grass Pollen

- Durham, 2012; 5-years
  - Adults (N = 634)
  - Sustained effect ages 18-65
- Maloney, 2014; 24 weeks
  - Adults (N = 1218) & Children (N = 283)
  - Assessed 1st grass pollen season efficacy in subjects aged 5-65 (N = 1501)
- Blakes, 2011; 24 weeks
  - Children (N = 344)
  - Assessed 1st grass pollen season efficacy in subjects aged 5-17

Ragweed

- Nolte, 2013; 52 weeks
  - Adults
  - Assessed peak ragweed pollen season efficacy vs placebo in individuals aged 18-30
- Creticos, 2013; 52 weeks
  - Adults
  - Assessed peak ragweed pollen season efficacy vs placebo in individuals aged 18-30

SLIT | Approved Tablet Doses

Oralair®
(Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3 and following</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-17</td>
<td>100 IR</td>
<td>2x100 IR</td>
<td>300 IR</td>
</tr>
<tr>
<td>18-65</td>
<td>300 IR</td>
<td>300 IR</td>
<td>300 IR</td>
</tr>
</tbody>
</table>

Grastek®
(Timothy grass)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-65</td>
<td>2800BAUs SL tablet Once daily</td>
</tr>
</tbody>
</table>

Ragwitek®
(Short ragweed)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-65</td>
<td>12 Amb a 1 unit SL tab Once daily</td>
</tr>
</tbody>
</table>

SLIT | Schedules

Pre-seasonal Treatment
- Treatment initiated 12-16 weeks prior to the allergen season
- Treatment maintained through the end of season
- Grass and ragweed tablet

Year-round Treatment
- Initiate ≥12 weeks before allergen season and continue throughout the year
- Does not appear to be superior to pre-seasonal treatment after the first year1-2
- Grass tablet

SLIT | Immunotherapy Tablets

Timothy Grass

Case 2 | William

- Chief Complaint: Allergic symptoms despite treatment
- Current Treatment: Environmental control, INAH, and INCS
- Allergen Testing (blood): Sensitization to timothy grass pollen

What are his treatment options at this time? SCIT vs SLIT-T?
**SLIT | Grass Pollen SLIT-T Improves Total Combined Symptoms**

- 23% vs 3.24
- 29% vs 3.33

TCS: Entire Season

TCS: Peak Season

**SLIT | Grass Pollen SLIT Improves Symptoms & QOL**

- Moderate reductions of symptoms (16%) and medication use (28%) for the grass allergen tablet 75,000 SQ-T compared with placebo
- Significantly better rhinoconjunctivitis quality of life scores
- Increased number of well days
- Efficacy was increased in the subgroup of patients who completed the recommended pre-seasonal treatment of at least 8 weeks before the grass pollen season (symptoms, 21%; medication use, 29%)
- No safety concerns were observed

**SLIT | Post-Treatment Disease Modification**

Long-term Confirmatory Trial (5-grass SLIT-T)

- 3 years of pre- and co-seasonal treatment → 2-year follow-up period
- Statistically significant difference between active and placebo at all points were observed
- ‘Disease modification’ is not in the label of this product

**SLIT | Immunotherapy Tablets**

Ragweed

**SLIT | Ragweed SLIT-T is Effective and Well-tolerated in Adults**

- 26% vs 8.46
- 26% vs 7.09

TCS: Peak Season

TCS: Entire Season

**SLIT | Ragweed SLIT-T is Effective and Well-tolerated in Adults**

- 24% vs 8.46
- 27% vs 7.09

TCS: Peak Season

TCS: Entire Season


**Case 2 | William**

- Incomplete relief from medications
- Work scheduling conflicts
- Shared decision making
- SLIT-T alternative immunotherapy option

41-year-old male consultant who travels for work

**SLIT-T | Dose Administration**

- Tablet should be placed under the tongue, where it dissolves
- Instruct the patient not to swallow for 1 minute
- Instruct the patient to avoid eating and drinking for 10 minutes
- Should be administered daily at approximately the same time each day
- The first dose will be administered in the office with a 30-minute observation period
- Observation period should be extended if significant AEs occur
- If further attention is required for the treatment of an AE and such treatment cannot be provided at the office/clinic, the patient should be transferred to an appropriate facility

**AIT | Adverse Events**

### SCIT
- Local (0.6-58%)
- Redness & induration at injection site
- Systemic (0.06-0.9%)
- Urticaria, GI upset, wheezing, and anaphylaxis
- Deaths at 1 per 2.5 million injections (3.4 deaths per year)
- Contraindications
- Uncontrolled asthma

### SLIT-T
- Local (0.2-97%)
- Oral itching and discomfort
- Systemic (0.056%)
- Urticaria, GI upset, wheezing, and anaphylaxis
- No reported deaths
- Contraindications
- Severe, unstable, or uncontrolled asthma

**Allergic Rhinitis | HDM**

**High variation in prevalence between countries, regions, and individual test centers**

- **World Prevalence**
  - 1-2% of the world’s population might be affected = 65-130 million people

- **European Community Respiratory Health Survey I**
  - Mean prevalence of sensitization to HDM = 21.7%
  - 21% overall prevalence for asthma with HDM sensitization with significant inter-population heterogeneity

- **Latino women in the US**
  - 34-37% mean prevalence of sensitization to HDM

- **Pediatric population in Taiwan**
  - > 80% prevalence

**SLIT | Immunotherapy Tablets**

**House Dust Mites (HDM)**

**SLIT | HDM Tablets Reduce Symptoms & Improve QOL in Adults and Children**

18-20% reduction in average adjusted symptom scores after 1 year of treatment (vs placebo)¹
- Ocular itching, nasal congestion and puritus, rhinorrhea, and sneezing
- Efficacy was maintained during AIT-free year

23% reduction in total combined rhinitis score in patients with HDM allergic asthma and rhinitis symptoms (vs placebo)²

- A significant difference was found for the total score of the Rhinitis Quality of Life Questionnaire with Standardized Activities RQLQ(S)
- No safety concerns were observed

**HDM SLIT-T is effective and safe in children**

- Significantly smaller wheals to D. pteronyssinus after 1 year of treatment with 56.50% mixture of D. pteronyssinus and O. farinaceus³
- Significant differences in symptom and medication scores after 2-year of treatment⁴

¹HDM SLIT-T is not approved by the FDA

AR is a significant medical burden
Allergen identification is important
Allergen skin tests are the best diagnostic test to confirm AR
Intranasal corticosteroids are the mainstay of treatment for most patients that present with AR
AIT is an effective immune-modulating treatment that should be recommended if pharmacologic therapy for AR is not effective or is not tolerated
SCIT is effective in the treatment of AR
SLIT-T is a new, effective treatment option in AR
- Demonstrated safety
- Suitable for pediatric use
- Administered at home