Update in Allergy

Mark A. Zacharek, MD, FACS, FAAOA
Associate Professor-Associate Program Director
Director Michigan Sinus Center
Department of Otolaryngology-Head and Neck Surgery
University of Michigan Health System
Disclosures

• None
Learning Objectives

- Gain an understanding of allergic inflammation and how it relates to diseases of the head and neck
- Explain the principles of diagnostic techniques and therapeutic options in the treatment of allergic diseases
Otolaryngology and Rhinitis

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Occupational rhinitis
- Gustatory rhinitis
- Autonomic dysfunction
- Pregnancy rhinitis
- Rhinitis medicamentosa
Allergic Rhinitis and Inflammation

- Otitis Media
- Asthma
- Rhinosinusitis
- Laryngitis
- Pharyngitis
- Conjunctivitis
- Atopic Dermatitis
- Urticaria
United States Skin Test Positive Responses

- Of 10,508 subjects (6-59 y/o; 3rd National Health & Nutrition survey) tested for 10 allergens, plus histamine & 50% glycerol saline controls
- 53.9% had 1 or more positive tests, with a median of 3
- Adjusted odds higher for ages 20-29 y/o, males, minority race, old &/or urban homes
- Many patients do not need therapy
- The patient’s severity of symptoms and physical exam findings are the determining factors

Allergic Rhinitis Demographics

- Prevalence: 17-22% in US with significant symptoms
- 6th most prevalent chronic disease in adults; most common in children
- Age and incidence:
  - <1% in infancy (primary food issues and atopic dermatitis)
  - Approximately 5-8% from ages 5-9 (asthma)
  - Allergic rhinitis peaks in late teens – early 20’s, and very slowly declines in later adulthood
Atopic march

Relative prevalence of symptoms according to age (many children exhibit symptoms simultaneously).
## Differential Diagnosis Considerations for Rhinitis

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Granulomatous</th>
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<tbody>
<tr>
<td>- Deviated Septum</td>
<td>- Granulomatosis with polyangiitis (Wegener’s)</td>
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<tr>
<td>- Adenoidal hypertrophy</td>
<td>- Sarcoidosis</td>
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<tr>
<td>- Foreign body</td>
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<tr>
<td>- Choanal atresia</td>
<td><strong>Mucociliary Defect</strong></td>
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<table>
<thead>
<tr>
<th>Tumor</th>
<th>CSF Rhinorrhea</th>
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<thead>
<tr>
<th>Infectious</th>
<th>GERD</th>
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<tr>
<td>- Viral, Bacterial, Fungal</td>
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</table>
Consider Past Medical History

- Asthma
- Eczema
- Food/Formula intolerance
- Recurrent/chronic otitis media
- History of food/drug anaphylaxis
- Surgery – T&A, PE Tubes, Sinus surgery
- Use of OTC allergy/cold formulations with decongestant
Also consider/review Family History

- Allergic Rhinitis
- Asthma, Aspirin sensitivity
- Angioedema, Urticaria
- Eczema
- Food intolerance

- Chance of having clinical atopy in offspring is 30% with one parent being atopic and over 50% with both parents having an atopic history
Social History

- Living accommodations
- How old/new is the home/apartment?
- Mold, danders, insects (cockroach)
- Basement or crawl space?
- Remodeling (carpet, insulation, painting)
- Airconditioning (central air, radiator heat, humidifier, filtration system changed recently?, ducts cleaned?)
- Indoor plants (mold)
Social History

- Tobacco use
- Alcohol use (vasodilation of nasal vasculature with alcohol)
- Exposure to young children and pets
- Occupational history (landscape architect, mill worker)
- Recent medication changes, diet changes
- Recent job relocation or environmental change
Physical Signs of Allergy

- Nose
- Throat
- Mouth
- Ears
- Eyes
- Skin
- Bronchial tree
- GI tract
Eye Exam and Allergic Disease

- Conjunctiva and lids
- Symptoms of pruritus, burning, tearing
- Acute allergic conjunctivitis – scleral injection, chemosis, lid edema, erythema, tearing, photophobia
- Chronic conjunctivitis – allergic shinners, long eye lashes, Dennie’s lines, thick mucous, cobblestone mucosa, lichenified lids, keratopathy
Allergic Conjunctivitis

- Allergic Shiners
- Allergic Salute
- Allergic crease
- Dennie's Lines
Signs and Symptoms of the nose and throat

• SAR- Sneezing, rhinorrhea, pruritis
• PAR – obstruction and post nasal drip

• Enlarged inferior and middle turbinates
• Boggy, bluish mucosa, edema
Allergic Signs and Symptoms: Skin

- Scaly, dry skin – lichenification
- Characteristic symptom is pruritus
- Clinical manifestation is eczema (adults antecubital and popliteal fossa and flexor surfaces).
- Children will have eczema in extensor surfaces
- Contact dermatitis, urticaria and angioedema
Allergy and the Lungs

- Do not forget patients who have allergic symptoms of the nose may have asthma
- Cough variant asthma
- Post URI, exercise induced, allergen exposure

- Proper screening requires thorough history and spirometry to measure lung function
Allergic Signs & Symptoms: Asthma

- Asthma = most common manifestation
- “Cough variant” asthma is mild form common in children
  - chronic, dry cough, especially with exertion or allergen exposure to cat or pollen
- consider laryngopharyngeal reflux in chronic cough
- Use stethoscope to auscultate anterior and posterior lung fields (Otolaryngologists are experts of the AIRWAY)
“Rule of 2”
Baylor Health Care System

Do you take your quick relief inhaler more than 2x/week?

Do you awaken at night with asthma more than 2x/month?

Do you refill your quick inhaler more than 2x/year?
Yes, Allergy is important to the Otolaryngologist……What about Immunology?
Immunology- Basic Terms and Definitions

• **Immunitas (Immunity)** – exemption granted to roman Senators

• **Innate immunity** – non-specific rapid response, unchanged with each exposure. No immunoglobulins or memory cells are generated.

• **Adaptive/acquired immunity** – requires prior exposure, two phases. 1. Rapid/immediate and delayed/late phase. These processes are directed by specific immunoglobulin and T/B lymphocyte activations.
**Functions of the Immune System**

- Recognition – Self vs non-self
- Surveillance – Neoplasm and Infection
- Memory – Clonal expansion from previously exposed and then specialized lymphocytes
- Amplification of response

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
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<tbody>
<tr>
<td>Complement</td>
<td>Antigen driven</td>
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<tr>
<td>Neutrophils</td>
<td>T-lymphocytes</td>
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<tr>
<td>Macrophages</td>
<td>B-lymphocytes</td>
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Mediators of Immune Response

**Cellular elements**
- Neutrophils
- Eosinophils
- Basophils
- Macrophages
- Lymphocytes

**Soluble elements**
- **Specific** = immunoglobulins – IgG, IgA, IgM, IgE, (IgD)
- **Non-specific**
  - Cytokines
  - Complement
  - Prostaglandins
  - Leukotrienes
  - Histamine
Cellular Function and Immune Response
- 2 General types

- **Director Cells** – orchestrate cellular and cytokinie complements of inflammation
  - Lymphocytes: T-Helper lymphocytes (Th cells), B-lymphocytes (B-cells), Cytotoxic T-lymphocytes (CTL), Monocytes, called Antigen Processing cells (APC)

- **Effector cells** – mediate local reaction via release of mediators (cytokine, inflammatory) & phagocytosis
  - Lymphocytes, called Natural Killer cells (NK cells),
  - Neutrophils, Eosinophils, Mast Cells, Basophils, Macrophages
Major Histocompatibility Class I Molecules

- MHC Class I Molecules – present on all nucleated cells
- Regulate immune response to endogenous epitopes
- Viral and tumor recognition
- Self vs non self
- Cytotoxic T-cells and natural killer cells
Major Histocompatibility Class II Molecules

- Regulation of immune response to exogenous pathogens
- Bacterial, viral epitopes presented by APC (Antigen presenting cells) to Helper T cells and B cells
T-Cell Surface “Clusters of Differentiation”
Helper versus Suppressor T-cells

- CD4 T-cells, called T-helper cells (Th1 and Th2) recognize antigen presented by MHC II molecules via antigen presenting cells, B-cells, macrophages.

- CD8 T-cells, called T-suppressor or cytotoxic cells recognize antigen presented by MHC I molecules. These cells target viruses, tumors, transplanted organs. They are also involved in down regulation of the immune response.
Antigen presenting cells (APC) and T-Helper Cell Activation
Cytokines

Low molecular weight proteins that bind to specific receptors and induce, enhance, inhibit genes and protein expression

4 Basic Families of Cytokines

1. **Type 1 or hematopoietic**
   - IL-4, TH2 differentiation & IgE production inducer
   - IL-5, production and survival of eosinophils
   - IL-13, similar spectrum of effects as with IL-4/5
   - IL-12, induce Th-1 differentiation response to infection

2. **Type II**
   - INF-y, pro-inflammatory
   - IL-10, down-regulates inflammatory cytokines

3. **Tumor Necrosis Factors**

4. **Chemokines** – Cellular attractants
**T-Helper Cells, Function and Cytokines**

**TH1**
- IFN-γ
- TNF-β
- IL-2

→ IgG2a Activated Macrophages

- Immune Defense against intracellular pathogens
- Unfavorable responses to autoantigens (diabetes, IBD)

**TH2**
- IL-4, IL-5
- IL-9, IL-13

→ IgE Eosinophils Mast Cells, Mucus

Immune defense against ectoparasites, gastrointestinal worms

Unfavorable responses to allergens (Allergy, Asthma)
Major Influences on Balance/Bias of the Immune System

Up-Regulation

Infection, Autoimmunity

TH1
INF-\(\gamma\), IL-2, TNF-B

TNF-a
IL-12

Allergy

TH2
IL-4, IL-5, IL-13

Immunotherapy

TGF-B
IL-10

Down-Regulation “Tolerance”
Antibody Isotype and Function

• **IgG** – major blood borne antibody response to pathogens; only antibody that crosses the placenta

• **IgA** – primary secreted antibody (with J-chain) in milk, mucous, tears, saliva, combats colonization and protects mucosal barriers (mouth, sinus, alimentary canal). Exists as a dimer

• **IgM** – first response to pathogens, can be secreted through mucous membranes (with J-chain). Exists as a pentamer

• **IgE** – binds to allergens and parasites, cross-linking on mast cells, basophils and eosinophils, causing degranulation

• **IgD** – antigen receptor present on naïve B-cells
## Gell and Coombs Classification of Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Gell and Coombs</th>
<th>Mechanism</th>
<th>Example</th>
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<tbody>
<tr>
<td>Type I</td>
<td>IgE-mediated</td>
<td>Anaphylaxis</td>
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<tr>
<td></td>
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<td>Urticaria</td>
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<tr>
<td>Type II</td>
<td>complement-mediated (IgG or IgM)</td>
<td>Hemolytic anemia</td>
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<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td>Type III</td>
<td>immune complex (IgG or IgM)</td>
<td>Serum sickness</td>
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<tr>
<td>Type IV</td>
<td>delayed hypersensitivity</td>
<td>Contact dermatitis</td>
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<td></td>
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<td>Morbilliform eruptions</td>
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<td></td>
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<td>Stevens-Johnson syndrome</td>
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Microcosms and Macrocosms

- The complexity of cellular interactions of the immune system are just as complex
Treatment options for Allergic Rhinitis

**Immunotherapy**
Offers the only true hope of a “cure”

**Avoidance**
Laudable in principle, Difficult in practice

**Pharmacotherapy**
Virtually all patients require some element
Allergy Therapy is a blending of Science and Art

The Science of allergy therapy
- Determining a safe starting dose
- Effective therapy

The Art of allergy therapy
- Escalation
- Safety vs Efficacy

"Better try it again—I got 3"
## Treatment options for Allergic Rhinitis

**Pharmacotherapy**
- Anticholinergics
- Decongestants
- Mast-cell stabilizers
- Antihistamines
- Anti-leukotrienes
- Monoclonal antibodies
- Anti-IgE (not FDA approved for Allergic Rhinitis TX alone)
- Anti-IL (5, 6, others) ongoing trials

**Immunomodulation**
- Corticosteroids
  - Systemic
  - Topical

**Immunotherapy**
- Subcutaneous
- Sublingual
- Other routes
Topical Decongestants

- Oxymetazoline, phenylephrine
- May be superior to intranasal topical steroids for nasal congestion
- Local stinging or burning, sneezing, dryness
- Sympathomimetic agonists for alpha 1, alpha 2 receptors resulting in vasoconstriction
- Prolonged use not recommended due to risk of developing rhinitis medicamentosa >7 days (rebound rhinitis)
Oral Decongestants

- Pseudoephedrine, phenylephrine
- Effective for nasal congestion
- Side effects include insomnia, irritability, palpitations
- Use with caution in patients with history of CAD, hypertension, bladder neck obstruction, acute angle glaucoma, history of CVA
- Not recommended for children less than 6 due to occurrence of psychosis, ataxia, hallucinations, death
Mucolytics

- Mechanism of action – increases parasympathetic tone thereby decreasing mucus viscosity and increasing volume
- Guaifenesin acts as an emetic
- Vagal stimulation
- Little objective evidence for use in allergic rhinitis
- Maximal dose for potential efficacy (2400mg/day)
Antihistamines

**H1 receptor antagonists effective in blocking early phase**

Early phase reaction is due to histamine induced inflammation
- Sneezing/itching
- Rhinorrhea
- Congestion

**Late Phase Reaction**
- Eosinophil recruitment
- Cell Adhesion
- Leukotrienes
Oral Antihistamines

- Fexofenadine, cetirizine, levocetirizine, desloratadine, loratadine
- Can be used for episodic symptoms
- Effective for control of rhinorrhea, sneezing, and itch
- Often the first line treatment for allergy rhinitis
- Antihistamines have little effect on nasal congestion
- Older 1st generation antihistamines should be avoided in the elderly (diphenhydramine, chlorpheniramine) as they can suppress cognition and effect memory
- 1st generation antihistamines have greater potency but greater anti-parasympathetic effects and cross the blood-brain-barrier
Oral antihistamines 2\textsuperscript{nd} Generation

- 2\textsuperscript{nd} generation antihistamines are preferred over older 1\textsuperscript{st} generation agents because they have less:
  - sedation
  - performance impairment
  - anticholinergic effects
Antihistamine nasal sprays

• **Azelastine**
  - Age 5 and older
  - Also indicated in non-allergic rhinitis

• **Olopatadine**
  - Age 6 and older
  - Onset of action 30 minutes

Efficacy of topical intranasal antihistamines > oral 2nd generation antihistamines, effective for congestion symptoms

Combination with intranasal corticosteroids reveals added benefit

Rhinitis practice parameter. JACI 2008; 122;s1-84
Topical intranasal antihistamines

- Rapid onset of action
- May be used on an episodic or PRN use
- Appropriate for use in mixed allergic and non-allergic rhinitis patients
- Bitter taste
- Sedation
Corticosteroids enter cell via lipophilic molecular structure
Binds to steroid receptor, conformation change allowing for transfer across nuclear membrane
Effecting mRNA transcription and resultant protein translation
Suppression of most cytokine and chemokine genes
Steroid Mechanisms

**Effector cells**
- Eosinophils
- Decreased recruitment
- Decreased immigration
- Increased apoptosis

**Basophils and Mast Cells**
- Decreased therefore
- Less histamine

**Director Cells**
- APCs - decreased
- T-lymphocytes
- Decreased CD4, CD8, CD25
- Decreased IL-4, IL-5
- Reduction of VCAM-1
- B-lymphocytes
- Cytokine expression
Intranasal corticosteroids

• Very effective for allergic rhinitis

• Effective for SAR and PAR (including nasal congestion)

• Appropriate for mixed allergic and non-allergic rhinitis

• Clinical efficacy equivalent for all currently available intranasal corticosteroids

• May benefit ocular allergy symptoms
Topical antihistamine + Topical steroid is better than one alone

Mechanisms of Immunotherapy

- Induction of Treg response
- IL-10 response/elevation (will be available as a serologic marker of immunotherapy effectiveness)
- Decreased Th2/Th1 ratio, decreased Th17
- Initial rise then gradual fall in allergen-specific IgE
- Class switching of B-cells to IgG1 then IgG4 (blocking antibody” and IgA2
Functions of Th1, Th2, Th17, and Treg cells

Immunologic changes during Allergy Immunotherapy

Early desensitization:
decrease in mast cell and basophil activity for degranulation and systemic anaphylaxis
T cell tolerance
induction of $T_{Reg}$ cells
suppression of Th2-Th1 cells

Late desensitization:
decrease in tissue mast cells and eosinophils
and release of their mediators

Burks et al. Update on allergy immunotherapy. J Allergy Clin Immunol; 131 (5). 1288-96
Immunologic changes during Allergy Immunotherapy

Burks et al. Update on allergy immunotherapy. J Allergy Clin Immunol; 131 (5). 1288-96
Immunotherapy – Other Avenues.....

- **Intranasal**
  - effective and safe per WHO (1998)
  - early nasal symptoms are bothersome
- **Bronchial**
  - marginal effectiveness, excessive risk
- **Oral**
  - immediately swallowed, marginal effectiveness
- **Sublingual (SLIT)**
  - both spit and swallow techniques
  - safe per WHO (1998) and effective per European Academy of Allergy and Immunology (2001)
- **Intralymphatic**
Sublingual Immunotherapy (SLIT)

- Less data than in subcutaneous immunotherapy
- No reported deaths due to SLIT, though reports due exist of anaphylaxis
- Possibly for children $\geq 3$ y/o
- Most studies involve self-administration of 1 allergen, (pollen)
- Doses ranges from (20-400X SCIT)
- No double blinded placebo controlled trials with multiple allergens compared to SCIT and analysis of treatment intervals
- European theme (monotherapy), currently no FDA approval for SLIT products in US
Novel Approaches to Allergy Immunotherapy

Burks et al. Update on allergy immunotherapy. J Allergy Clin Immunol; 131 (5). 1288-96
Resources

• American Academy of Otolaryngic Allergy (AAOA) Basic and Advanced Courses (July and December respectively)
• Fall AAO-HNS and AAOA meetings with courses/primers on otolaryngic allergy.
• www.aaaaai.org/practice-resources/statements-and-practice-parameters
• Consider becoming a Fellow of the AAOA
• Visit aaoa@aaoadf.org
Thank you