Pharmacotherapy for Allergic Rhinitis

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Learning Objectives

- Describe the basic mechanism of action for different types of allergy medications
- Discuss the available options for allergic rhinitis therapy
- Summarize a basic treatment strategy for allergic rhinitis

Management of Allergic Rhinitis

- Environmental control
- Pharmacotherapy
- Immunotherapy

Pharmacotherapy for Allergic Rhinitis

The selection of pharmacotherapy for a patient depends on multiple factors:

- Symptom profile
- Cost/availability
- Patient compliance/ease of administration
- Response to previous treatment
- Pathophysiology of disease
- Associated medical conditions
- Side effect profile

What’s Available?

- Targeted therapy
  - Decongestants
  - Mucolytics
  - Antihistamines
  - Anti-cholinergics
  - Anti-leukotrienes
  - Mast-cell stabilizers
- Immnomodulation
  - Steroids
  - Systemic
  - Topical
  - Immunotherapy
  - Monoclonal Abs
  - Anti-IgE
  - Anti-IL

Disclosures:

- None
Topical Decongestants

- Oxymetazoline, phenylephrine
- May be superior to INS for nasal congestion
- Local stinging or burning, sneezing, dryness
- Prolonged use not recommended

Wallace DV. JACI 2008;122:S1-84

Topical Decongestants

- Sympathomimetic Agonist for α1 and α2 receptors, resulting in vasoconstriction
- Onset of action: 5 min
- Duration: > 6h
- Local potency greater than with systemic
- Risks
  - Tachyphylaxis
  - Rhinitis medicamentosa
  - Little evidence of adverse effects if used only 3–7 days


Oral Decongestants

- Pseudoephedrine, Phenylephrine
- Effective at relieving nasal congestion
- Side effects = insomnia, irritability, palpitations
- Phenylephrine appears less effective than pseudoephedrine
- Use with caution in patients with hypertension, bladder neck obstruction, closed angle glaucoma, hyperthyroidism, cerebrovascular or cardiovascular disease
- Use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, death. Therefore use in children under 6 with caution.

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Oral Decongestants

- Choices
  - Pseudoephedrine
  - Phenylephrine
  - Stimulate α1 & β receptors
  - Pharmacokinetics
    - Peak levels: 1–3 h
    - T1/2: 3–4 h
    - Urinary clearance
  - Risks
    - HTN, ASCAD
    - Glaucoma
    - Hyperthyroidism
    - MAO inhibitors
    - Urinary retention
    - Stroke

Mucolytics

- Mechanism of action
  - Increases parasympathetic tone
  - Decreases viscosity
  - Increases volume
  - Guaifenesin acts as an emetic
  - Vagal stimulation
  - Little objective evidence of efficacy in AR
  - Must treat at maximal dose for potential efficacy
  - 2400 mg/day


Antihistamine: Effect of Histamine

- H1 Receptors
  - Early phase Reaction
    - Sneezing
    - Rhinorrhea
    - Congestion
  - Late phase Reaction
    - EOS recruitment
    - Cell adhesion
    - Leukotrienes
  - Late Phase Reaction

Vasodilation (Congestion)
Trigeminal Irritation (Sneeze)
Vascular Permeability (Rhinorrhea)
Oral Antihistamines

- **Fexofenadine, cetirizine, levocetirizine, desloratadine, loratadine**
- Can be used for episodic symptoms
- Effective for control of rhinorrhea, sneeze, and itch
- Often the first line treatment for allergic rhinitis
- Little effect on nasal congestion

Rhinitis Practice Parameter. JACI 2008;122:S1-84

Oral Antihistamines

- Less effective than INS; equivalent to INS for ocular symptoms
- Generally ineffective for non-allergic rhinitis; therefore other options better for mixed rhinitis
- Among the 2nd gen agents, no one agent has conclusively demonstrated superior efficacy

Rhinitis Practice Parameter. JACI 2008;122:S1-84

Oral Antihistamines

- 2nd generation antihistamines preferred over 1st generation agents because less:
  - sedation
  - performance impairment
  - anticholinergic effects
- Less effective for nasal congestion than other options

Rhinitis Practice Parameter. JACI 2008;122:S1-84

Antihistamines: Cognitive Effects

- Antagonism of central H1 receptors affect cognitive skills
  - Sedation
  - Decreased cognitive performance
  - Motor coordination
  - Central interpretation of vestibular input
  - Adverse effect on intellectual and motor performance and may occur in absence of subjective awareness by patient

Oral Antihistamines: Cognitive Effects

- 1st Generation
  - Chlorpheniramine
  - Clemastine
  - Diphenhydramine
  - Hydroxyzine
  - Promethazine
- 2nd Generation
  - Acrivastine
  - Bilastine
  - Cetirizine
  - Desloratadine
  - Ebastine
  - Fexofenadine
  - Levocetirizine
  - Loratadine

Clin Exp Allergy 2000;30:891-916
Topical Intranasal Antihistamines

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

- **Olopatadine**
  - Age 6 and older
  - Onset of action on-label = 30 minutes

**Azelastine nasal spray in Fexofenadine failures**


**Topical Intranasal Antihistamines**

- Azelastine, Olopatadine
- Efficacy ≥ oral 2nd generation antihistamines
- Efficacy for congestion symptoms
- Combination with intranasal corticosteroid shows added benefit

Rhinitis Practice Parameter. *JACI* 2008;122:S1-84

**Topical Intranasal Antihistamines**

- Rapid onset of action = episodic or PRN use
- Efficacy compared to INS not established similar over short term
- Appropriate option for mixed rhinitis
- Bitter taste and/or sedation

Rhinitis Practice Parameter. *JACI* 2008;122:S1-84

**Azelastine vs. Cetirizine for SAR**

- Multi-center RDBPCT, 2 week treatment period
- Improvement in TNSS was significantly greater with azelastine nasal spray compared with cetirizine (29.3% vs 23.0% improvement, respectively; P =0.015).
- RQLQ score was significantly improved with azelastine nasal spray compared with cetirizine (P =0.049).


**Intranasal Antihistamines**

Olopatadine vs. Fluticasone


Anticholinergics

- Ipratropium bromide
  - Decreases parasympathetic tone
  - Decreases watery rhinorrhea
  - Does not reduce:
    - Congestion
    - Irritation
    - Itching
    - Sneezing
  - 0.03% and 0.06% strengths

Anticholinergics

- Anti-cholinergic side effects
  - Use with caution in patients with narrow angle glaucoma, prostatic hyperplasia, bladder neck obstruction

Leukotrienes

- First identified in the 1930’s
  - Known collectively as slow reacting substances of anaphylaxis (SRS-A)

  - Inflammatory mediators produced locally by:
    - Eosinophils
    - Macrophages
    - Basophils
    - Monocytes

Leukotrienes

- Cysteinyl leukotrienes
  - LTC4, LTD4, LTE4
  - Promote inflammatory cell recruitment and activation
  - Enhance the production of cytokines
  - Induce vascular leakage and vasodilation
  - Stimulate mucus secretion
  - Decrease mucociliary clearance

Haberal and Corey. OTO-HNS 2003;129:274-9

Leukotrienes

- LTD4 instillation causes dose dependent increase in nasal mucosal blood flow and nasal airway resistance

- LTD4 topical application increases nasal secretions

- LTD4 is 5000 times more potent than histamine at inducing nasal congestion, has 3-fold greater duration of action

Peters-Golden M, Henerson WR. Annals Allergy Asthma Immunol 2005;94:609-618
Leukotriene Modifiers

- Synthesis Inhibitors (5-lipoxygenase)
  - Zileuton
- Receptor Antagonists (CysLT1 receptor)
  - Montelukast
  - Zafirlukast

Leukotriene Receptor Antagonists

- Effective for SAR and PAR
- Comparable efficacy to antihistamines; use with antihistamines may be additive
- Montelukast approved down to 6 mos.
- Approved for both rhinitis and asthma; May be useful in patients with both conditions

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Oral LTRAs vs. Antihistamines

Steroids

- Mechanisms
- Clinical Effect
  - CS enters cell
  - Lipophilicity
  - Binds to steroid receptor
  - Transcription
  - mRNA
  - Translation
  - Protein
- Effect: Downregulate inflammatory responses by binding to intracellular glucocorticoid receptors
  - receptors undergo conformational changes upon activation, enter nucleus
  - bind with glucocorticoid response elements located on anti-inflammatory genes
  - activated genes transcribe messenger RNA for anti-inflammatory proteins
  - activated glucocorticoid receptors suppress the transcription of most cytokine and chemokine genes

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**Steroids: Mechanisms**
- **Effector Cells**
  - Eosinophils
    - Decreased recruitment
    - Decreased immigration
  - Basophils & Masts
    - Decreased
    - Less histamine
- **Director Cells**
  - APCs - decreased
  - T-lymphocytes
    - CD4, CD8, CD25
  - IL-4, IL-5
  - Down-regulation of VCAM-1
  - B-lymphocytes
  - Cytokine expression

**Systemic Corticosteroids**
- A short course may be appropriate for severe symptoms, especially if nasal polyposis present
- Can be administered parenterally, or injected intranasally
- Recurrent administration of systemic corticosteroids has potential for long term corticosteroid side effects

**Intranasal Corticosteroids**
- Very effective medications for AR
- Effective for all symptoms of SAR and PAR, including congestion
- Appropriate choice for mixed rhinitis
- Clinical response about equal for all currently available INS
- May benefit ocular allergy symptoms; similar to oral antihistamine

**Intranasal Corticosteroids**
- More effective than oral antihistamine ± LT antagonist
- Onset of action b/w 3-12 hrs. More effective with continuous use
- Not generally associated with systemic side effects
- Older agents associated with growth suppression in children
- May cause bleeding, irritation, septal perforation

**Intranasal Corticosteroids**
- Beclomethasone dipropionate
- Budesonide
- Ciclesonide
- Flunisolide
- Fluticasone propionate
- Fluticasone furoate
- Mometasone furoate
- Triamcinolone

**In Vitro Inhibition of IL-4**
- Indicator of potency of agent
  - Most
    - Fluticasone
    - Mometasone
    - Least
    - Beclomethasone
    - Triamcinolone
    - Intermediate
    - Budesonide

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Topical Antihistamine + Topical Steroid


Topical Nasal Steroids: Safety

- Potential adverse effects
  - Intranasal effects
  - Burning
  - Dryness
  - Nosebleeds
  - Possible mechanical complication
  - Septal perforation - rare

- Intranasal effects
  - Burning
  - Dryness
  - Nosebleeds

- Systemic risks
  - Glaucoma or cataracts
  - Bone loss, growth retardation
  - Other systemic corticosteroid risks

- Insufficient data to base estimate of risk

- Reasonable to inform patients that the risks of these outcomes are likely small, although the impact over a lifetime is not yet understood.

Beclomethasone: Pediatric Growth

Skoner Pediatrics 2000;105:E23

Mometasone: Pediatric Growth

Schenkel Pediatrics 2000;105:E22
Safety in Pediatrics

- Multiple studies have demonstrated none or minimal growth suppression with topical nasal steroid use in children, especially with newer agents having lower bioavailability.

Allergic Rhinitis Guidelines

- Pharmacotherapy recommendations:
  - Intranasal antihistamines for improvement in quality of life
    - Strong recommendation
  - Second generation oral antihistamines for sneezing and itching
    - Strong recommendation
  - Intranasal antihistamines for all type of allergic rhinitis
    - Option
  - Oral leukotriene receptor antagonists SHOULD NOT be used for primary treatment
    - Strong recommendation AGAINST
  - Combination therapy for inadequate monotherapy response
    - Option

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Thank you