Pharmacotherapy for Allergic Rhinitis

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2012 AAOA Basic Course
Disclosures:

• Alcon Labs, Consultant
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 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
  - Anticholinergics
  - Anti-leukotrienes
  - Mast-cell stabilizers

- **Immunomodulation**
  - Steroids
    - Systemic
    - Topical
  - Immunotherapy
  - Monoclonal Abs
    - Anti-IgE
    - Anti-IL
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.

Wallace DV. JACI 2008;122:S1-84
Oral Decongestants

I Choices
  I Pseudoephedrine
  I Phenylephrine

I Stimulate $\alpha_1$ & $\beta$ receptors

I Pharmacokinetics
  I Peak levels: 1-3 h
  I $T_{1/2}$: 3-4 h
  I Urinary clearance

I Risks
  I HTN, ASCAD
  I Glaucoma
  I Hyperthyroidism
  I MAO inhibitors
  I Urinary retention
  I 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
    - Sneeze/itch
    - Rhinorrhea
    - Congestion
      - Smooth muscle contraction
  - Late Phase Reaction
    - EOS recruitment
    - Cell adhesion
    - Leukotrienes

- Vasodilatation (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 2\textsuperscript{nd} gen agents, no one agent has conclusively demonstrated superior efficacy
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 H$_1$ 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:

- **1\textsuperscript{st} Generation**
  - Chlorpheniramine
  - Clemastine
  - Diphenhydramine
  - Hyroxyzine
  - Promethazine

- **2\textsuperscript{nd} Generation**
  - Acrivastine
  - \textit{Bilastine}
  - Cetirizine
  - Desloratadine
  - Ebastine*  
  - Fexofenadine
  - Levocetirizine
  - Loratadine
Oral antihistamines are less effective for nasal congestion.

Clin Exp Allergy 2000;30:891-9.16
Antihistamine Nasal Sprays

Azelastine

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

Olopatadine

• Age 6 and older
• Onset of action on-label = 30 minutes
Azelaistine 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: rapid onset of action

Nasal antihistamines and steroids may have equivalent efficacy

Olopatadine vs. Fluticasone for SAR

* P = 0.043

Anticholinergics

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

• **Indications**
  • Common cold
  • Seasonal allergic rhinitis
  • Age 5 and older

• **Other uses**
  • Nonallergic rhinitis
  • “Skier’s Nose”
  • Gustatory rhinorrhea
  • Senile Rhinorrhea
Ipratropium Cautions

- 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)

• Isolated in 1983 (Samuelson, *Science* 220;568-75,1983)
  – Inflammatory mediators produced locally by:
    • Eosinophils
    • Basophils
    • Mast Cells
    • Macrophages
    • Monocytes
Biologic Effects of Leukotrienes in Rhinitis

- Cysteinyl leukotrienes
  - \( \text{LTC}_4, \text{LTD}_4, \text{LTE}_4 \)
  - 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: impact on nasal obstruction

- 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

Wallace DV. JACI 2008;122:S1-84
Oral Leukotrienes vs. H1 Antihistamine: day and night symptoms

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<th>Study or subcategory</th>
<th>SMD (random) 95% CI</th>
<th>Weight %</th>
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<td>Nayak et al, 2002</td>
<td>16.39 0.02 (-0.17, 0.21)</td>
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<td>Philip et al, 2002</td>
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<td>van Adelsberg et al, 2003</td>
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<td>van Adelsberg et al, 2003</td>
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<tr>
<td>Total (95% CI)</td>
<td>100.00 0.04 (-0.04, 0.11)</td>
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</tbody>
</table>

- Test for heterogeneity: $\chi^2 = 2.54$, $df = 4$ ($P = .64$), $I^2 = 0\%$
- Test for overall effect: $Z = 0.90$ ($P = .37$)
Steroids
Steroids: Mechanism of Action

• Clinical Effect
  – CS enters cell
    • Lipophilicity
  – Binds to steroid receptor
  – Transcription
    • mRNA
  – Translation
    • Protein
Steroids: Mechanisms

- 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
Steroids: Mechanisms

- **Effector Cells**
  - Eosinophils
    - Decreased recruitment
    - Decreased immigration
    - Increased apoptosis
  - Basophils & Masts
    - Decreased
    - Less histamine

- **Director Cells**
  - APCs - decreased
  - T-lymphocytes
    - CD\(_4\), CD\(_8\), CD\(_25\)
    - 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

Wallace DV. JACI 2008;122:S1-84
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

Wallace DV. JACI 2008;122:S1-84
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

Wallace DV. JACI 2008;122:S1-84
Intranasal Corticosteroids

- Beclomethasone dipropionate
- Budesonide
- Ciclesonide
- Flunisolide
- Fluticasone propionate
- Fluticasone furoate
- Mometasone furoate
- Triamcinolone
In Vitro Inhibition of IL-4 in Response to Glucocorticoids

- Indicator of potency of agent
  - Most
    - Fluticasone
    - Mometosone
  - Least
    - Beclomethasone
    - Triamcinolone
  - Intermediate
    - Budesonide

Umland, J Allergy Clin Immun 1997;100:511-9
Topical antihistamine + Topical steroid is better than either alone

Topical Nasal Steroids
Safety
• Potential adverse effects
  – Intranasal effects
    • Burning
    • Dryness
    • Nosebleeds
      – Possible mechanical complication
    • Septal perforation - rare
Topical Nasal Steroids
Safety

• 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.
Topical Nasal Steroids

Safety

• Growth suppression in pediatric use
  – Shown at usual dose with beclomethasone
  – Not seen at one year with mometasone and fluticasone
  – Reasonable precautions:
    • Inform parents of possible effects, but reassure
    • Use lowest effective dose
    • Watch additive effect with multiple preparations
      – Intranasal plus inhaled steroids
Beclomethasone: Effect upon Growth in Pediatric Patients

N = 100

Skoner Pediatrics 2000;105:E23
Mometasone: Effect upon Growth in Pediatric Patients

N = 98

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

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
Thank you