ARIA
(Allergic Rhinitis and its Impact on Asthma)

GLORIA
(Global Resources In Allergy)

ATBP
(at iba pa)

Zenaides T. Wi, M.D, FPCS, FPSOHNS
Some thoughts:

“Clinical guidelines are systematically developed statements designed to help practitioners and patients make decisions about appropriate health care for specific circumstances”...

“the goal of guidelines is their wide dissemination within the medical community in order to improve patient’s care…”

... Jean Bousquet, EAACI, Brussels, July 1999
CLINICAL GUIDELINES IN ALLERGIC RHINITIS

- Guidelines in Making Guidelines
- Evidence Based Medicine VS Expert Opinion
- Common Sense
- Cochrane Collaboration
- Narrow the Gap between Clinical Research and Clinical Practice
Guidelines should be:

- Simple
- Adapted to clinical practice and drug availability in various countries
- Should not represent a yardstick but rather a help for physicians
Let me see...it all began this way...
It all began this way……...

- Before 1994- pocket studies on Rhinitis, Sinusitis, etc.
- 1995 to the present- start of serious and widespread discussions/studies on the relationship of the upper and lower airways: Rhinitis and Asthma, United Airways, One Airway One Disease…etc
- 2000- EAACI Consensus Statement on the Treatment of Allergic Rhinitis
- 2001- ARIA (Allergic Rhinitis and Its Impact on Asthma), same group who made the 2000 EAACI Consensus agreed on the ARIA.
- 2003- GLORIA (Global Resources in Allergy) WAO (World Allergy Org.) initiated an educational program to disseminate worldwide the ARIA and other allergy issues.
What will I share with you today?

- Discussion on History and Allergic Rhinitis
- ARIA and GLORIA
- DESLORATADINE (AERIUS)
- MOMETASONE (NASONEX)
Heto na si GLORIA!
Section 1: Allergic Rhinitis

an educational program of:
GLORIA resource documents

- Allergic Rhinitis and Its Impact on Asthma (ARIA): *JACI 2001:56: 813-824*
- Contemporary Approaches to Ocular Allergy Management: *American College of Allergy, Asthma and Immunology, 1998.*
- World Allergy Forum program series: *WAO 2000-2003*
Allergic rhinitis is clinically defined as a symptomatic disorder of the nose, induced after allergen exposure, by an IgE mediated inflammation of the nasal membranes.
Major symptoms of allergic rhinitis: ARIA

- Rhinorrhea
- Nasal Obstruction
- Nasal Itching
- Sneezing
Allergic rhinitis: Relationship to allergic conjunctivitis

- 42% of patients with allergic rhinitis experience symptoms of allergic conjunctivitis
- Conjunctivitis is a typical feature of the patient with intermittent symptoms due to seasonal pollens
Allergic Rhinitis: Co-morbidity sinusitis

- Strong association (>50%) between sinusitis and allergic rhinitis in children and adults
- Otitis media is a common co-morbidity
Allergic rhinitis – relationship to asthma: ARIA

- Most patients with allergic and non-allergic asthma have rhinitis
- Many patients with rhinitis have asthma
- Allergic rhinitis is associated with and also constitutes a risk factor for asthma
- Many patients with allergic rhinitis have increased non-specific bronchial hyperreactivity
Classifications of allergic rhinitis

- Intermittent (*seasonal - acute - occasional*)
  - Occasional symptoms lasting < four days per week or ≤ four weeks
- Persistent (*perennial - chronic - long duration*)
  - Symptoms lasting > four days per week and > four weeks
New classification of allergic rhinitis: Severity - ARIA

- Mild
  - Normal sleep
  - Normal daily activities, sport, leisure
  - Normal work and school
  - No troublesome symptoms
New classification of allergic rhinitis: Severity - ARIA

- Moderate - Severe
  - Abnormal sleep
  - Impairment of daily activities, sport, leisure
  - Problems caused at work or school
  - Troublesome symptoms
<table>
<thead>
<tr>
<th>ARIA Classification</th>
<th>Intermittent</th>
<th>Persistent</th>
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<tr>
<td></td>
<td>&lt; 4 days per week</td>
<td>≥ 4 days per week</td>
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<tr>
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<td>or &lt; 4 weeks</td>
<td>and ≥ 4 weeks</td>
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</table>

**Mild**

- normal sleep
- & no impairment of daily activities, sport, leisure
- & normal work and school
- & no troublesome symptoms

in untreated patients

**Moderate-severe**

- *one or more items*
  - abnormal sleep
  - impairment of daily activities, sport, leisure
  - abnormal work and school
  - troublesome symptoms
Differential diagnosis of rhinitis - 1

- Allergic
- Infectious: Viral, bacterial, fungal
- Non-infectious, non-allergic rhinitis
- Drug-induced: Aspirin, other medications
- Occupational: May be both allergic or non-allergic
- Hormonal: Puberty, pregnancy, menstruation, endocrine disorders
- Other causes: Foods, gustatory, irritants, emotion, Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES), gastro-oesophageal reflux, atrophic
Differential diagnosis of rhinitis - 2

- Vasomotor rhinitis - persistent non-allergic rhinitis; vascular and/or neurological dysfunction of nasal mucosa
  - Females (90%), 40-60 years
  - Nasal congestion and post-nasal drip in response to change in temperature, humidity, barometric pressure; smells such as perfume, cigarette smoke, paint and ammonia; emotional stress
Differential diagnosis of rhinitis - 3

- Polyps
- Mucociliary Defects
- Cerebrospinal Rhinorrhoea
- Tumors - Benign, Malignant
- Mechanical - Anatomical abnormalities, Foreign Body
- Granulomas - Sarcoid, Infectious, Wegener’s, Midline Granuloma
Concomitant pathology: Allergic and non-allergic rhinitis

- About 40% of patients have pure allergic rhinitis
- About 25% have pure non-allergic rhinitis
- About 35% have mixed rhinitis - a mixture of both diseases
Epidemiology of allergic rhinitis: Children

- Prevalence of rhinitis symptoms, International Study of Asthma and Allergies in Childhood *Asher et al, 1995*: between 0.8% and 14.95% in 6-7 year olds between 1.4% and 39.7% in 13-14 year olds
- Low prevalence: Indonesia, Georgia, Greece
- High prevalence: Australia, UK and Latin America
Epidemiology of allergic rhinitis: Adults

- No equivalent to ISAAC study
- National surveys show prevalence rates between 5.9% (France) and 29% (United Kingdom), mean 16%
- Persistent (perennial) rhinitis more common in adults than children
Globally important allergens

- House dust mites
- Grass, tree and weed pollen
- Pets
- Cockroaches
- Molds
Diagnosis of allergic rhinitis: Essential

- Detailed personal and family allergic history
- Intranasal examination – anterior rhinoscopy
- History of eye symptoms
- Allergy skin tests performed by allergist, eg, skin tests and/or
- Measurement of allergen specific IgE antibody in serum (Radioallergosorbent tests)
Allergy skin prick testing

- Skin prick test / positive result
Radio-allergosorbent tests

CAP RAST scores indicate specific IgE levels where 0-absent (<0.35 KUa/1), 1-low (0.35-0.7 KUa/1), 2-moderate (0.7-3.5 KUa/1), 3-high (3.5-17.5KUa/1), 4-very high (17.5-50 KUa/1), 5-very high (50-100 KUa/1), 6-very high (>100 KUa/1).

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<td>f-- <em>D. pteronyssinus</em> (mite)</td>
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<td>f-- <em>A. fumigatus</em> (mold)</td>
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<tr>
<td>f- Cat</td>
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Nasal endoscopy
Nasal secretions/scrapings for cytology (done rarely)
Nasal challenge test with allergen, including rhinomanometry
CT scan
Allergic Rhinitis: Additional investigations

- Strong association (>50%) between sinusitis and allergic rhinitis in children and adults
- If sinusitis history present – fever, headache, facial pain, mucopurulent discharge, cough and fatigue – consider CT scan of sinuses
# Signs and symptoms of rhinitis vs. sinusitis

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<tr>
<td>Itching</td>
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<td>-</td>
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<tr>
<td>Rhinorrhea-clear</td>
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<td>+</td>
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<tr>
<td>Rhinorrhea-purulent</td>
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<tr>
<td>Post-nasal drip</td>
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<tr>
<td>Headache</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Facial pressure</td>
<td>+</td>
<td>++ or +++</td>
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<tr>
<td>Anosmia, Hyposmia</td>
<td>+ or ++</td>
<td>++++ or ++++</td>
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<td>Cough</td>
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<td>+++</td>
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<tr>
<td>Throat clearing</td>
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<td>+++</td>
</tr>
<tr>
<td>Fever</td>
<td>- or +</td>
<td>++</td>
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</table>
Additional investigations recommended:

- History of asthma
- Chest examination
- Lung function before and after bronchodilator
- Tests for non-specific bronchial hyperreactivity
Immunopathology of allergic rhinitis: Early phase reaction

- Mast cell degranulation, release of histamine, leukotriene C4/D4, platelet activating factor, prostaglandin D2, give rise to acute symptoms:
  - Nasal Itch
  - Sneezing
  - Acute Rhinorrhoea
Immunopathology of allergic rhinitis: Precursors of late phase reaction

- Mast cell secretion of cytokines and chemokines
- Stimulation of endothelial cells by histamine, leukotrienes and PAF to secrete cytokines and chemokines
- Activation of counter-ligands on endothelial cells to interact with blood cells which roll, adhere and then transmigrate
Immunopathology of allergic rhinitis: Late phase reaction

- Sub-epithelial cell accumulation of CD4(+) Th2 lymphocytes, monocytes, eosinophils and basophils which become activated by the cytokine/chemokine network as well as by antigen stimulation of high and low affinity IgE receptors
Immunopathology of allergic rhinitis: Histamine

- Pre-formed mediator
- Released from activated mast cells
- Major mediator in early phase reaction
- Causes sneezing, itching, rhinorrhea, nasal obstruction
- Pro-inflammatory activity
Immunopathology of allergic rhinitis: Leukotrienes

- Early generated mediators
- Participate in both immediate and late reactions
- Cause nasal obstruction, mucus secretion, vasodilation, inflammatory cell recruitment
Immunopathology of allergic rhinitis: Minimal persistent inflammation

- Minimal persistent inflammation is present even in the absence of symptoms when patients are exposed to pollen or perennial allergens.
Mediators and symptoms in allergic rhinitis

**Immediate rhinitis symptoms**
- Itch, sneezing
- Watery discharge
- Nasal congestion

**Chronic rhinitis symptoms**
- Nasal blockage
- Loss of smell
- Nasal hyperreactivity
Step-wise management of allergic rhinitis

- **Step 1**: Allergen Avoidance and Environmental Control
- **Step 2**: Pharmacotherapy
- **Step 3**: Immunotherapy
Management of allergic rhinitis: Allergen avoidance and environmental control

- House dust mites:
  - Provide adequate ventilation to decrease humidity
  - Wash bedding regularly at 60°C
  - Encase pillow, mattress and quilt in allergen impermeable covers
  - Use vacuum cleaner with HEPA filter (when available)
  - Dispose of feather bedding
  - Replace carpets with linoleum or wooden floors
  - Remove curtains, pets and stuffed toys from bedroom
Management of allergic rhinitis: Allergen avoidance and environmental control

◆ Pollen
  - Very difficult to avoid!
  - Remain indoors with windows closed at peak pollen times
  - Wear sunglasses
  - Use air-conditioning, where possible
  - Install car pollen filter
Management of allergic rhinitis: Allergen avoidance and environmental control

Pet Allergens

- Exclude pets from bedrooms and, where possible, from home
- Vacuum carpets, mattresses and upholstery regularly
- Wash pets regularly
Cockroach Allergens

- Eradicate cockroaches with appropriate insecticide
- Eliminate dampness, cracks in floors, ceilings, cover food; wash surfaces, floors, fabrics to remove allergen

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Molds

• Ensure dry housing
• Use ammonia to remove mold from bathrooms and other wet spaces
Pharmacotherapy of allergic rhinitis: Topical antihistamines

◆ Azelastine and levocabastine
  • Rapid onset of action (15 minutes)
  • Twice daily administration
  • Recommended for organ-limited disease
  • May be used as needed continuously
  • Useful in non-allergic rhinitis as well
  • Good safety profile
Pharmacotherapy of allergic rhinitis: First generation oral antihistamines

- Chlorpheniramine, diphenhydramine, promethazine, tripolidine
- Use limited by sedative and anticholinergic effects
Pharmacotherapy of allergic rhinitis

Properties required of ideal new generation oral antihistamines

- No sedation
- Once daily administration
- Rapid onset and 24 hour duration of action
- No interaction with drugs, foods, alcohol
- Additional anti-allergic effect
Pharmacotherapy of allergic rhinitis: New generation oral antihistamines

- Acrivastine, azelastine, cetirizine, desloratadine, ebastine, epinastin, fexofenadine, ketotifen, levocetirizine, loratadine, mizolastine

- First line treatment for intermittent or mild persistent allergic rhinitis
Pharmacotherapy of allergic rhinitis: New generation antihistamines

- Reduce sneezing, itching, runny nose
- Some, but less significant, effects on congestion
- Generally preferred by patients
Pharmacotherapy of allergic rhinitis: Anti-allergic compounds

- Disodium cromoglycate (DSCG) and nedocromil
  - Less effective than antihistamines
  - Require frequent administration: DSCG four times/day, nedocromil two times/day
  - Excellent safety profile for use in children and pregnancy
Pharmacotherapy of allergic rhinitis: Anti-cholinergic compounds

- Ipratropium bromide
  - Effective in controlling watery nasal discharge but not sneezing or obstruction.
  - Unwanted effects may include nasal dryness, irritation and burning.
Pharmacotherapy of allergic rhinitis: Decongestants

- Oral Tablets
  - Less effective than sprays: no rhinitis medicamentosa
  - Effective when combined with an oral antihistamine
  - Usually avoided in: children <1 year, pregnancy, hypertension, cardiopathy, prostatism, glaucoma
Pharmacotherapy of allergic rhinitis: Decongestants

- **Topical Sprays**
  - Very effective in treating nasal obstruction
  - Limit treatment to 3-10 days depending on physician recommendations
  - Application for >10 days may lead to unwanted side effects, e.g., rhinitis medicamentosa
Pharmacotherapy of allergic rhinitis: Antileukotrienes

- Less effective than inhaled corticosteroids and antihistamines
- May have additive effect with antihistamines
- Efficacy in aspirin-induced rhinitis and asthma
- Expensive, impractical for most
Pharmacotherapy of allergic rhinitis: Topical corticosteroids

- Beclomethasone dipropionate
- Budesonide
- Fluocortinbutyl
- Flunisolide
- Fluticasone propionate
- Mometasone furoate
- Triamcinolone acetonide
Pharmacotherapy of allergic rhinitis: Topical corticosteroids

- Most potent anti-inflammatory agents
- Effective in treatment of all nasal symptoms including obstruction
- Once or twice daily administration
- Superior to antihistamines for all nasal symptoms
- First line pharmacotherapy for moderate-severe persistent allergic rhinitis
Pharmacotherapy of allergic rhinitis: Topical corticosteroids

- Occasional unwanted effects
- Rarely affect HPA axis (some exceptions)
- Perforation of the nasal septum has been reported
- One study reports decrease in growth in children; other studies have not reported the same finding
Pharmacotherapy of allergic rhinitis: Systemic corticosteroids

- Short courses (< 5 days) can be prescribed for severe refractory symptoms
- Use with caution in children and in pregnancy if no alternative is available
- Concern regarding osteoporosis should limit use
- Intramuscular injections should be avoided
Pharmacotherapy of allergic rhinitis: Injection allergen immunotherapy

- Recommended for clinically relevant IgE mediated disease. May involve multiple allergens; usually restricted to two allergens in Europe.
- Risk-to-benefit ratio must be considered in all cases.
- Highly effective in selected patients.
- Injection immunotherapy for allergic rhinitis may prevent allergic asthma from developing.
Pharmacotherapy of allergic rhinitis: Injection allergen immunotherapy

- Effective when optimally administered
- Standardised therapeutic vaccines favoured
- Subcutaneous immunotherapy alters natural course of disease
- Should be performed by trained personnel, and patients must be monitored after injection according to local guidelines
Pharmacotherapy of allergic rhinitis: High-dose sublingual-swallow immunotherapy

Controlled studies show that high-dose sublingual swallow immunotherapy is a viable alternative to injection allergen immunotherapy for mild intermittent allergic disease.
Evidence-based step-wise guidelines to manage pharmacotherapy of allergic rhinitis

- A rational basis to commence and manage pharmacotherapy
- Relate clinical symptoms to underlying pathology
- Allergen avoidance and environmental control underpin all pharmacotherapy
- Clinical judgement determines starting point and appropriate combination of pharmacotherapies
- When symptoms improve, step down pharmacotherapy
Modes and sites of action of allergic rhinitis pharmacotherapies

Immediate rhinitis symptoms
- Itch, sneezing
- Watery discharge
- Nasal congestion

Chronic rhinitis symptoms
- Nasal blockage
- Loss of smell
- Nasal hyperreactivity

**Allergen avoidance**
- Allergen
- Mast cell
- Histamine
- Leukotrienes
- Prostaglandins
- Bradykinins, PAF

**Anti-IgE**
- IgE
- IL-4
- VCAM-1
- GM-CSF

**Immuno-therapy**
- T cell (mast cell)
- IL-3, -5

**Antihistamines**
- Sodium cromoglycate
- Immune reactions
- Immediate rhinitis symptoms
- Chronic rhinitis symptoms

**Sodium cromoglycate**
- IL-3, -5
- GM-CSF

**Steroids**
- IL-4
- VCAM-1

**Sodium cromoglycate**
- Immediate rhinitis symptoms
- Chronic rhinitis symptoms
# Step-wise guidelines for pharmacotherapy of intermittent allergic rhinitis: Adults, mild

Increase pharmacotherapy in a step-wise fashion until adequate control is achieved

## Step 1
- Oral or nasal anti-histamines
- or
- DSCG/nedocromil

## Step 2
- Nasal Cortico-steroids

## Step 3
- Maintain treatment with Nasal cortico-steroids and oral/nasal anti-histamines
Step-wise guidelines for pharmacotherapy of intermittent allergic rhinitis: Adults, moderate-severe

Increase pharmacotherapy in a step-wise fashion until adequate control is achieved

**Step 1**
- Nasal corticosteroids, and/or
- Oral/nasal antihistamines

**Step 2**
- Add further symptomatic treatment, eg, short course topical or oral decongestant
- Short course of oral corticosteroids
- Consider Immunotherapy
**Step-wise guidelines for pharmacotherapy of persistent allergic rhinitis: Adults, mild**

Increase pharmacotherapy in a step-wise fashion until adequate control is achieved.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
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<tbody>
<tr>
<td>Oral/nasal anti-histamines</td>
<td>Nasal corticosteroids</td>
<td>Maintain treatment with Nasal corticosteroids and anti-histamines</td>
<td>Allergist or ENT Specialist Assessment</td>
</tr>
</tbody>
</table>
## Step-wise guidelines for pharmacotherapy of persistent allergic rhinitis: Adults, moderate-severe

In resistant cases where no other pathology is seen:

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
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<tbody>
<tr>
<td><strong>Resistant nasal blockage:</strong></td>
<td><strong>Consider surgical intervention</strong></td>
</tr>
<tr>
<td>Decongestant/short course oral corticosteroids</td>
<td>eg, for deviated nasal septum,</td>
</tr>
<tr>
<td></td>
<td>unresponsive chronic sinusitis, allergic fungal sinusitis</td>
</tr>
</tbody>
</table>

**Resistant rhinorrhoea:**
- Nasal ipratropium bromide and consider immunotherapy
Step-wise guidelines for pharmacotherapy of persistent allergic rhinitis: Adults, moderate-severe

Increase pharmacotherapy in a step-wise fashion until adequate control is achieved

Step 1
Nasal corticosteroids (moderate disease)
plus
anti-histamines (severe disease)

Step 2
Further Examination by Allergist or ENT specialist
Step-wise guidelines for pharmacotherapy of persistent allergic rhinitis: Children

Increase pharmacotherapy in a step-wise fashion until adequate control is achieved

- **Step 1**: Oral/nasal antihistamines or nasal cromones
- **Step 2**: Nasal corticosteroids in recommended dose
- **Step 3**: Consider immunotherapy
allergen avoidance indicated when possible

pharmacotherapy safety effectiveness easy to be administered

immunotherapy effectiveness specialist prescription may alter the natural course of the disease

patient's education always indicated

costs
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>directly based on randomised controlled trials and meta-analyses</td>
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<tr>
<td><strong>B</strong></td>
<td>evidence from at least one controlled study without randomisation <em>or</em> extrapolated recommendation from category A evidence</td>
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<tr>
<td><strong>C</strong></td>
<td>evidence from at least one other type of quasi-experimental study <em>or</em> extrapolated recommendation from category A or B evidence</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>evidence from expert committee reports <em>or</em> opinions <em>or</em> clinical experience of respected authorities, <em>or</em> both</td>
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**Statement of evidence: Strength of evidence - Shekelle et al, BMJ 1999**
### Strength of evidence for treatment of rhinitis

#### ARIA

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<tr>
<th>Intervention</th>
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<th>PAR children</th>
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<td>allergen avoidance</td>
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# Medications of allergic rhinitis

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<tr>
<th>Medication</th>
<th>sneezing</th>
<th>rhinorrhea</th>
<th>nasal obstruction</th>
<th>nasal itch</th>
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Mild intermittent rhinitis

ARIA

Options (not in preferred order)

- oral or intranasal anti-H1
- intranasal decongestants
- oral decongestants (not in children)
Moderate-severe intermittent rhinitis

Mild persistent rhinitis

ARIA

Options (not in preferred order)

- oral or intranasal anti-H1
- oral anti-H1 + decongestant
- intranasal CS
- (chromones)

Patient should be re-assessed after 2-4 wks
ARIA

Step-wise approach

- intranasal CS as a first line treatment
- if major blockage: add short course of oral CS or decongestant

Re-assess after 2-4 weeks

- if symptoms present add:
  - oral anti-H1 (± decongestants)
  - ipratropium
Conjunctivitis rhinitis

ARIA

Options (not in preferred order)

- oral or ocular anti-H1
- ocular chromones
- saline

Do not use ocular CS *without care and eye examination*
Treatment of allergic rhinitis (ARIA)

**Allergic Rhinitis and its Impact on Asthma**

- **mild intermittent**
  - intra-nasal steroid
  - local cromone

- **moderate severe intermittent**
  - oral or local non-sedative H1-blocker
  - intra-nasal decongestant (<10 days) or oral decongestant
  - allergen and irritant avoidance

- **mild persistent**

- **moderate severe persistent**
  - immunotherapy
Pharmacotherapy of allergic disease: Future directions

>75% of allergic asthmatics have rhinitis

>40% of allergic rhinitis patients have allergic conjunctivitis

Humanized monoclonal antibodies against IgE, e.g. omalizumab are effective for treatment of moderate to severe allergic asthma. Such therapy:

- Decreases free IgE levels and down-regulates IgE receptors on basophils

(cont’d on next slide)
Pharmacotherapy of allergic disease: Future directions, cont’d.

- Inhibits the late phase allergic reaction following allergen bronchial challenge
- Preliminary study indicates omalizumab is effective for nasal and ophthalmic symptoms of intermittent and persistent allergic rhinitis
Ayos....commercial naman tayo.
Structures

Loratadine

Desloratadine
Desloratadine:

- Is a highly potent, selective H₁ antagonist
- Has a long dissociation time
  - $t_{1/2} > 6$ hours
- Shown to inhibit the release of pro-inflammatory mediators at clinically relevant concentrations
Desloratadine
Triple Mode of Action

Antihistaminic

Anti-allergic

Desloratadine

Anti-inflammatory
AERIUS Efficacy in SAR

Efficacy End Points

Nasal
- Rhinorrhea
- Nasal stuffiness
- Nasal congestion
- Nasal itching
- Sneezing

Non-nasal
- Itching/burning eyes
- Tearing/watery eyes
- Red eyes
- Itching of ears or palate

2-Week Study
AERIUS SAR Studies

- No serious adverse events

- Adverse events profile from SAR program

<table>
<thead>
<tr>
<th></th>
<th>AERIUS</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>2%</td>
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So let us see the evolution…

- ARIA…
- AERIA…
- AERIAS…

And finally

- AERIUS…Thank You.
Salamat po!