Morbidity and Co-morbidities for Children with Allergic Rhinitis

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Financial Disclosure:
Research grant/Consultant/Speaker

<table>
<thead>
<tr>
<th>Abbott</th>
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<tr>
<td>Alcon</td>
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<td>Stallergenes</td>
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<td>GlaxoSmithKline</td>
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</table>
High prevalence of allergic rhinitis (AR)

- AR is the most common of all chronic conditions in children in the USA (Storms, 1997)

- AR develops before age 20 in 80% of cases

- **Worldwide prevalence of AR:**
  - 0.8 to 14.9% in the 6–7 year-old age group
  - 1.4 to 39.7% in the 13–14 year-old age group (ISAAC, 1998)

- **USA prevalence of AR**
  - up to 42% for 6-yrs olds (Wright, 1994)

- **Rising prevalence**
  - 100% increase in each of last 3 decades in developed countries (Linneberg, 2000)

- Children frequently lack the ability to verbalize their symptoms

Children Diagnosed with Nasal Allergies: 1 in 7

Age at Diagnosis of Children with Allergic Rhinitis

Impact on health

- Symptoms and signs of AR

- Co-morbidities associated with AR
  - Conjunctivitis
  - Rhinosinusitis
  - Otitis
  - Dental malocclusions
  - Asthma

- Quality of life with AR

Parent Reports of Children’s Nasal Allergy Symptoms During the Worst Month in Past Year


N=500
Parent Reports of Severity of Nasal Allergy Symptoms – Extremely or Moderately Bothersome

Faces of Allergy

- Itchy eyes
- Allergic Shiners
- Allergic eyes
- Itchy nose
- Allergic crease
- Allergic Salute
Impact on health

Co-morbidities associated with the disease
- Conjunctivitis
- Rhinosinusitis
- Otitis media
- Dental malocclusions
- Asthma

Prevalence of Concomitant Conditions Experienced in Previous Week by Children With and Without AR

- Children with AR have a 10-fold increased incidence of sinus problems compared with children without AR
- Children with AR have > 3-fold more skin rashes, fever, migraines, earaches, frequent respiratory infections, and conjunctivitis compared with children without AR

National survey interviewed parents of children 4-9 years of age and parents and children over 10 years of age. Number of children in the household between 4-17 years of age diagnosed with AR, nasal allergies, or “hay fever.” The calculation of overall prevalence of the disease in children was based on all children who were reported by parents to have been diagnosed with nasal allergies of all households.

Meltzer EO, et al. Burden of allergic rhinitis
J Allergy Clin Immunol 2009;124:S43-70
Secondary Symptoms of Nasal Allergies Experienced Most Days/Wk or Every Day During Worst Month

Secondary Symptoms of Nasal Allergies

Sinus Problems in the Past Week

<table>
<thead>
<tr>
<th>Children With AR</th>
<th>Children Without AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>4</td>
</tr>
</tbody>
</table>

Snoring Most Nights or Every Night

<table>
<thead>
<tr>
<th>Children With AR</th>
<th>Children Without AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>9</td>
</tr>
</tbody>
</table>

* p < 0.001
Surgery Potentially Related to AR

### Nasal Allergies Contribute to Other Upper-Airway Problems

<table>
<thead>
<tr>
<th>Pain or pressure</th>
<th>Patients or parents, %</th>
<th>Fold difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AR</td>
<td>No AR</td>
</tr>
<tr>
<td>Pain or pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache*</td>
<td>54</td>
<td>19</td>
</tr>
<tr>
<td>Face*</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Ear*</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubes placed†</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Tonsils and/or adenoids removed‡</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Sinus problems*</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Snoring*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every day</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Most days</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

AR = Allergic rhinitis.

* $P < 0.001$

† $P < 0.05$

‡ $P < 0.01$

**Pediatric Allergies in America Survey**
Prevalence of Asthma in Children With and Without AR

- Children with AR have a ≥3-fold increased incidence of asthma diagnosis and asthma symptoms than children without AR (*p<0.001)

Impact on quality of life

AR can have a profound impact on the overall and various dimensions of quality of life (QoL) of children.

AR has been associated with:
- Sleep disturbances
- Emotional problems
- Activity limitations
- Mental impairments
- Social interruptions
- Practical disruptions

Meltzer EO. J Allergy Clin Immunol 2001;108:S45–53;
General Health Comparison by Parents of Children With (n=500) and Without (n=504) Allergic Rhinitis


*P<0.05
Parent Perceptions on the Effect of Nasal Allergy Symptoms on Children’s Sleep

- Sleeping: 40%* (Allergies), 7% (No allergies)
- Difficulty in getting to sleep: 32%* (Allergies), 12% (No allergies)
- Waking up during the night: 26%* (Allergies), 8% (No allergies)
- Lack of a good night's sleep: 29%* (Allergies), 12% (No allergies)

*P<0.05

Meltzer EO, et al. Burden of allergic rhinitis
J Allergy Clin Immunol 2009;124:S43-70
More Than 65% of Children Are Tired and Irritable Because of Allergy Symptoms

Meltzer EO, et al. Burden of allergic rhinitis
J Allergy Clin Immunol 2009;124:S43-70
Parents Perceptions of Overall Feelings of Well Being in Children With (n=500) and Without (n=504) Allergic Rhinitis


*P<0.05
Parent Perceptions of Allergy/Health Effects on School Absenteeism and Presenteeism, and Avoidance of Daily Activities in Children With and Without Allergic Rhinitis


*P<0.05
Parent Perceptions on the Effect of Nasal Allergy Symptoms on Children’s Productivity

Thinking about your child’s ability to do things (he/she) wants to do—on a scale of 0 to 100, where 100 means 100% able:
Where would you rank (his/her) ability on days when (he/she) doesn’t have nasal allergy symptoms?
Where would you rank your child’s ability on the same scale of 0 to 100 when (his/her) nasal allergies are at their worst?

Parent Perceptions on the Effect of Nasal Allergy Symptoms on Type and Amount of Work Performed by Children

- Accomplished less: 23%* (Allergies), 10% (No allergies)
- Cut down on amount: 22%* (Allergies), 10% (No allergies)
- Difficulty in performing: 23%* (Allergies), 10% (No allergies)
- Been limited in kind of work or other activities: 21%* (Allergies), 11% (No allergies)

*P<0.05

Parent Perceptions on the Effect of Nasal Allergy Symptoms on Children’s Activities

Organized sports or exercising
- Allergies: 32%
- No allergies: 10%

Outdoors activities
- Allergies: 31%
- No allergies: 7%

Going out/Playing with friends
- Allergies: 29%
- No allergies: 6%

Having pets
- Allergies: 27%
- No allergies: 4%

Doing well in school
- Allergies: 26%
- No allergies: 9%

Doing things with family
- Allergies: 23%
- No allergies: 5%

School activities
- Allergies: 17%
- No allergies: 5%

Indoor activities
- Allergies: 12%
- No allergies: 5%

*P<0.05

Meltzer EO, et al. Burden of allergic rhinitis
J Allergy Clin Immunol 2009;124:S43-70
Percentage of Children Receiving Medications to Treat Nasal Allergy Symptoms

Change of Children’s Prescription Medication

- Never: 40%
- Only rarely: 31%
- Every few years: 10%
- Once a year: 8%
- Several times a year: 8%
- Not sure: 3%
- Only rarely: 31%
- Never: 40%

Pharmacotherapy for Children

- Oral antihistamines
- Intranasal antihistamines
- Intranasal corticosteroids
Oral Antihistamines

- 1\textsuperscript{st} generation agents
- 2\textsuperscript{nd} generation agents
  - Cetirizine
  - Levocetirizine
  - Loratadine
  - Ebastine
  - Desloratadine
  - Fexofenadine
Key efficacy fexofenadine SAR study

Aim:
- Assess effect of fexofenadine HCl 30 mg BID compared with placebo across all SAR symptoms in children 6-11 years old

Methods:
- Placebo-controlled, parallel-group study conducted in 148 centers in 15 countries
- 935 children randomized to fexofenadine HCl 30 mg BID (n=464) or placebo (n=471) for 2 weeks
- Primary efficacy variable
  - Mean change from baseline in the average PM-reflective TSS throughout the double-blind treatment period.

Efficacy results:
- Significant reductions in TSS and all individual symptom scores compared with placebo at all time points

Efficacy in children 6–11 years: TSS

Baseline scores for fexofenadine and placebo, respectively, were: 7-pm reflective TSS 6.8, 7.1; 7-am reflective TSS 6.5, 6.7. Data are from the mITT population

TSS= Total Symptom Score

Daytime
Night-time

Mean change from baseline in TSS

* p≤0.0001

* p≤0.0001

Placebo (n=469)
Fexofenadine HCl 30 mg BID (n=463)

Fexofenadine relieves all AR symptoms

Mean change in 12-hr PM reflective individual symptom scores

- Sneezing
- Rhinorrhea
- Itchy nose/mouth/throat/ears
- Itchy watery/red eyes
- Nasal congestion

Placebo = 469
Fexofenadine = 463

* p<0.01
** p<0.001
*** p≤0.0001

Most Bothersome Attributes of Nasal Allergy Medications in Children

- Dripping down throat: 10% Extremely, 19% Moderately
- Bad taste: 12% Extremely, 16% Moderately
- Burning: 7% Extremely, 8% Moderately
- Drying feeling: 5% Extremely, 9% Moderately
- Headaches: 5% Extremely, 1% Moderately
- Drowsiness: 4% Extremely, 7% Moderately

Adverse-event profile of fexofenadine 30 mg BID similar to placebo

Most frequent treatment-emergent adverse events (TEAEs) (>1%)*

![Bar chart showing the frequency of TEAEs for fexofenadine and placebo]

The frequency of TEAE was similar between the fexofenadine (18.3%) and the placebo (18.7)

Safety of fexofenadine in children: pooled safety analysis

- Data pooled from three, double-blind studies examining fexofenadine HCl 30 mg and 60 mg BID in children 6–11 years (n>800)
  - Fexofenadine HCl 30mg BID, n = 673
  - All fexofenadine treated groups, n =1110
  - Placebo, n = 700

- Incidences of AEs, and discontinuations due to AEs, were low and similar across treatment groups

- 24.4% of subjects in the placebo group reported AEs compared with 24.1% for fexofenadine HCl 30 mg BID, and 28.4% for all fexofenadine-treated groups

Safety of fexofenadine in children 6-11 y: pooled safety analysis

- The most common AE overall was headache
  - 4.3%, (30/700), 5.8% (39/673) and 7.2% (80/1110) for placebo, fexofenadine HCl 30 mg BID and any fexofenadine dose, respectively

- Treatment-related AEs were similar across treatment groups
  - No sedation detected
  - No clinically relevant changes in vital signs data
  - No effect on QTc interval

Safety and tolerability of fexofenadine in younger children

- **Children aged 2–5 yrs (Milgrom 2007)**
  - Placebo-controlled, parallel-group study of fexofenadine HCl 30 mg BID (n=222), or placebo (n=231) x2 weeks
  - **No clinically meaningful differences between fexofenadine and placebo in pattern or intensity of TEAEs**

- **Children aged 6 mos–2 yrs (Hampel, 2007)**
  - Two placebo-controlled, parallel-group studies
    - Fexofenadine HCl 30 mg BID (n=108) or placebo (n=110)
    - Fexofenadine HCl 15 mg BID (n=85) or placebo (n=89)
  - **AE profile of fexofenadine similar to placebo**
    - Number of AE
      - **Fexofenadine: 40.0%; placebo: 42.7%**
      - **Fexofenadine: 35.2%; placebo: 52.7%**

Fexofenadine is indicated in SAR in children 2 to 11 years of age.
In urticaria from 6 months of age

Intranasal Antihistamines

- **Azelastine**
  - No efficacy trials in children <12 years
  - Dose 1 spray/nostril BID 5-11 years*
  - Dose 1-2 sprays/nostril BID >12 years*

- **Olopatadine**
  - No efficacy trials in children <12 years
  - Dose 1 spray/nostril BID 6-11 years*
  - Dose 2 sprays/nostril BID >12 years*

*Approved by FDA
Olopatadine 0.6% Nasal Spray for SAR

Nasal Symptoms

BID Tx for 14 Days in patients ≥ 12 yr with fall SAR

% Change in rTNSS**

* p<0.05 olopatadine vs. placebo
** rTNSS=Total Nasal Sx Score (0=absent to 3/severe)

Most bothersome attributes of nasal allergy medications in children:

- Dripping down throat: 10% (extremely), 19% (moderately)
- Bad taste: 12% (extremely), 16% (moderately)
- Burning: 7% (extremely), 8% (moderately)
- Drying feeling: 5% (extremely), 9% (moderately)
- Headaches: 5% (extremely), 1% (moderately)
- Drowsiness: 4% (extremely), 7% (moderately)

# Olopatadine Nasal Spray Adverse Events in Pediatric Patients 6 to 11 Years of Age

<table>
<thead>
<tr>
<th>Adverse Events &gt;1%</th>
<th>Olopatadine Nasal Spray (N=298)</th>
<th>Vehicle Nasal Spray (N=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis*</td>
<td>17 (5.7%)</td>
<td>11 (3.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (4.4%)</td>
<td>11 (3.7%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (2.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Bitter taste</td>
<td>3 (1.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (1.3%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (1.3%)</td>
<td>0 (0.0%)</td>
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</tbody>
</table>

*Defined as a “fleck of blood” apparent on nasal examination.

**Note:**

PATANASE® Nasal Spray Package Insert
Intranasal Corticosteroids

- Aqueous intranasal corticosteroids
  - Beclomethasone dipropionate
  - Budesonide
  - Ciclesonide
  - Flunisolide
  - Fluticasone furoate
  - Fluticasone propionate
  - Mometasone furoate
  - Triamcinolone acetonide

- Aerosol intranasal corticosteroids (HFA)
  - Beclomethasone dipropionate
  - Ciclesonide

Drugs@FDA. US Food and Drug Administration.
Intranasal Corticosteroids Provide Relief to Pediatric Nasal Allergy Sufferers

Does your child’s current prescription nasal spray give relief from all symptoms, most symptoms, some symptoms, or no symptoms?
(Base: Uses Intranasal Corticosteroid, n=129)

Available at: http://www.myallergiesinamerica.com/Alergies_website_v13.swf
Comparable Efficacy of Intranasal Steroids (TA-FP) in SAR in Adults (N=352 x3 weeks)

Adverse events occurred in 138 TAA patients (80.2%) and 152 FP patients (84.4%)

Primary efficacy variable: mean total nasal symptom score (sum individual nasal symptom scores)

Triamcinolone is significantly preferred by patients compared to other nasal corticosteroids

Mean nasal spray evaluation questionnaire scores two minutes after administration

(Adapted from Bachert C, 2002)

Multicenter, DB, controlled, cross-over study in 95 patients (ITT population) with Allergic Rhinitis (Perennial or Seasonal)

Triamcinalone Significantly Decreases SAR Nasal Index in Children ages 6-11 years

No serious adverse events reported:
31 in triamcinolone, 22 in the placebo reported AEs
Most were mild

Multicenter, DB, PBO controlled, 2 –weeks study in children 6-11 yrs
Primary endpoint: Nasal index: sum of symptom scores: nasal stuffiness, nasal discharge, sneezing.

Triamcinolone Significantly Decreases PAR Symptoms in Children ages 2-5 years

Possibly related to study medication in the DB period: similar between the groups: triamcinolone:13 [5.5%]; placebo:20 [8.4%]

Multicenter, DB, 4- weeks (open phase 6 months), PC study in children ages 2-5 years with PAR 4-point scale: (0=symptom absent to 3=severe)
Primary endpoint: Change from baseline in the mean daily instantaneous total nasal symptom score (TNSS) over the double-blind treatment period

Weinstein S, Ann Allergy, Asthma Immunol, 2009: 102, 339-347
Children with SAR (Ages 6-11y) and PAR (Ages 3-11y): Changes from Baseline Congestion Score Days 1-15; 1-29

P<0.05 MFNS (mometasone furoate aqueous nasal spray) vs Pbo
Study 1 = SAR; Study 2 = PAR
Congestion = Primary end point

# Children with SAR (Ages 6-11y) and PAR (Ages 3-11y): Adverse Events

<table>
<thead>
<tr>
<th>AEs reported by ≥5% of patients, n (%)</th>
<th>Study 1 (SAR)</th>
<th>Study 2 (PAR)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MFNS 100 mcg (n=135)</td>
<td>MFNS 100 mcg (n=190)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=136)</td>
<td>Placebo (n=191)</td>
</tr>
<tr>
<td>Fever, 9 (7%)</td>
<td>Fever, 11 (8%)</td>
<td></td>
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<tr>
<td>Headache, 30 (22%)</td>
<td>Headache, 26 (19%)</td>
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<tr>
<td>Asthma, 8 (6%)</td>
<td>Asthma, 12 (9%)</td>
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<tr>
<td>Coughing, 7 (5%)</td>
<td>Coughing, 11 (8%)</td>
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<tr>
<td>Epistaxis, 12 (9%)</td>
<td>Epistaxis, 10 (7%)</td>
<td></td>
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<tr>
<td>Pharyngitis, 9 (7%)</td>
<td>Pharyngitis, 14 (7%)</td>
<td></td>
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<tr>
<td>Vomiting, 7 (5%)</td>
<td>Vomiting, 7 (5%)</td>
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<td></td>
<td>Coughing, 27 (14%)</td>
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<td></td>
<td>Headache, 24 (13%)</td>
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<td></td>
<td>Fever, 16 (8%)</td>
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<tr>
<td></td>
<td>Pharyngitis, 14 (7%)</td>
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<td>Coughing, 33 (17%)</td>
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<td>Fever, 15 (8%)</td>
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<tr>
<td></td>
<td>Pharyngitis, 14 (7%)</td>
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<tr>
<td></td>
<td>Epistaxis, 17 (9%)</td>
<td></td>
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<tr>
<td></td>
<td>Viral infection, 14 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

Triamcinolone vs Placebo: Serum cortisol levels are not altered

Mean increase in morning serum cortisol level after cosyntropin infusion in the cosyntropin-evaluable population. Error bars represent SD.

Multicenter, randomized, double-blind, placebo-controlled, parallel-group study immediately followed by an open-label extension period

Weinstein S, Ann Allergy, Asthma Immunol, 2009: 102, 339-347
Triamcinalone vs Placebo: Stature Remains Stable Throughout 6 months Treatment Period

Distribution of 353 patients by stature-for-age percentile at baseline and at the end of the 6-month open-label period based on the National Center for Health Statistics, Centers for Disease Control and Prevention (NCHS CDCP) standards

Weinstein S, Ann Allergy, Asthma Immunol, 2009: 102, 339-347
Monocenter, open-label, non-randomized, prospective study of the long term effect of triamcinolone on statural growth in 39 children from 6-14 years in a 2 year-study

Thank you!