Update in Asthma Treatment

Jennifer DeMore, MD
Asthma Partnership Forum
June 4, 2019
Disclosure

- Nothing to disclose
Overview

- Prevalence
- Development
- Evaluation & Monitoring
- Medications & Immunomodulation
- Side Effects
Asthma Overview

- Prevalence of current asthma 8%\(^1\)
- 34 million Americans diagnosed by health professional during lifetime\(^2\)
- 10 million physician office visits every year - 9,789,350 in 2017\(^1\)
- 200,000 hospitalizations per year - 188,968 in 2017\(^1\)
- 3564 deaths attributed to asthma\(^1\)

1. [https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm](https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm) (Accessed 5/2019)
Asthma Prevalence

Asthma Prevalence By Age Group

Current asthma prevalence is higher among children (8.4% vs 7.7%)²

1 Data 2001-2003; 2007 CDC Surv. Summ on Asthma
2 www.cdc.gov/asthma/most_recent_national_asthma_data.htm (Accessed 5/2019)
Development of Asthma in Children

- Infections
- Allergens
- Genetics
- Environment
Infections

- Viruses
  - RSV
    - Palivizumab prevent
  - Rhinovirus
    - Rhinovirus most frequent cause of exacerbations

- *Chlamydia* and *Mycoplasma* species

Kelly JT *J Allergy Clin Immunol.* 2008;122:671–682
>50% of HRV detected in sick infants were previously unrecognized strains - including 9 strains from new HRV group

HRV-C compared with any other virus was associated with increased risk of respiratory hospital admission

Cox 2013 AJRCCM: 1358.
Wheezeing and Infection

- 20% children have at least 1 episode of LRI associated with wheezing in the 1st year of life
  - 70% of these are associated with viral infections
- Viral respiratory infection cause wheezing in 50% of all children during first 3 years of life

Allergens in Asthma Pathogenesis

- Sensitization
  - house dust mite\(^1\)
  - cockroach\(^2\)
  - *Alternaria* species\(^3\)
  - possibly cat\(^4\)

- Wide variety of inhaled allergens can provoke asthma symptoms

\(^1\) Celedon *J Allergy Clin Immunol*. 2007;120:144–149
\(^3\) Bush RK *J Allergy Clin Immunol*. 2004;113:227–234
\(^4\) Arbes *J Allergy Clin Immunol*. 2007;120:1139–1145
Genetics

- Genetically classified as complex disorder
  - Hundreds of genetic association studies
  - Gene environment interactions
- Genes found associated with asthma
  - at least 5 independent reports

Ober C *Genes Immun.* 2006;7:95–100
Donata Vercelli *Nature Reviews Immunology* 8, 169-182 (March 2008)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Function and pathway</th>
<th>Common variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1</td>
<td>1p13.3</td>
<td>Environmental and oxidative stress — detoxification</td>
<td>+/null</td>
</tr>
<tr>
<td>FLG</td>
<td>1q21.3</td>
<td>Epithelial barrier integrity</td>
<td>Arg510X, 2282del4</td>
</tr>
<tr>
<td>IL10</td>
<td>1q31-q32</td>
<td>Immuno-regulation</td>
<td>−1082A/G, −571C/A</td>
</tr>
<tr>
<td>CTLA4</td>
<td>2q33</td>
<td>T-cell-response inhibition and immunoregulation</td>
<td>−118C/T, Arg130Gln</td>
</tr>
<tr>
<td>IL13</td>
<td>5q31</td>
<td>T2 effector functions</td>
<td>−589C/T, +33C/T</td>
</tr>
<tr>
<td>IL4</td>
<td>5q31</td>
<td>T2 differentiation and IgE induction</td>
<td>−1721G/A, −260C/T</td>
</tr>
<tr>
<td>CD14</td>
<td>5q31</td>
<td>Innate immunity — microbial recognition</td>
<td>Glu420Lys</td>
</tr>
<tr>
<td>SPINK5</td>
<td>5q32</td>
<td>Epithelial serine protease inhibitor</td>
<td>Arg16Gly, Gln27Glu</td>
</tr>
<tr>
<td>ADRB2</td>
<td>5q31-q32</td>
<td>Bronchial smooth-muscle relaxation</td>
<td>5383_5397del</td>
</tr>
<tr>
<td>HAVCR1</td>
<td>5q33.2</td>
<td>T-cell-response regulation — HAV receptor</td>
<td>−444A/C</td>
</tr>
<tr>
<td>LTC4S</td>
<td>5q35</td>
<td>Cysteinyl leukotriene biosynthesis — inflammation</td>
<td>Ncol (intron I)</td>
</tr>
<tr>
<td>LTA</td>
<td>6p21.3</td>
<td>Inflammation</td>
<td>−308B/A, −857C/T</td>
</tr>
<tr>
<td>TNF</td>
<td>6p21.3</td>
<td>Inflammation</td>
<td>Multi-SNP alleles</td>
</tr>
<tr>
<td>HLA-DRBI</td>
<td>6p21</td>
<td>Antigen presentation</td>
<td>Multi-SNP alleles</td>
</tr>
<tr>
<td>HLA-DQBI</td>
<td>6p21</td>
<td>Antigen presentation</td>
<td>Multi-SNP alleles</td>
</tr>
<tr>
<td>HLA-DPBI</td>
<td>6p21</td>
<td>Antigen presentation</td>
<td>Slow acetylation SNPs</td>
</tr>
<tr>
<td>GPRA</td>
<td>7p14.3</td>
<td>Regulation of cell growth and neural mechanisms</td>
<td>Haplotypes</td>
</tr>
<tr>
<td>NAT2</td>
<td>8p22</td>
<td>Detoxification of drugs and carcinogens</td>
<td>Il6B1LLeu, Gly237Glu</td>
</tr>
<tr>
<td>FCER1B</td>
<td>11q13</td>
<td>High-affinity Fc receptor for IgE</td>
<td>38A/G</td>
</tr>
<tr>
<td>CCL6</td>
<td>11q12.3-q13.1</td>
<td>Epithelium-derived anti-inflammatory protein</td>
<td>Il6B105Val</td>
</tr>
<tr>
<td>GSTP1</td>
<td>11q13</td>
<td>Environmental and oxidative stress — detoxification</td>
<td>−6567T/G, −137G/C</td>
</tr>
<tr>
<td>IL1B</td>
<td>11q22.2-22.3</td>
<td>Induction of IFNγ and TNF</td>
<td>2964G/A, (GT)n exon I</td>
</tr>
<tr>
<td>STAT6</td>
<td>12q13</td>
<td>IL-4 and IL-13 signalling</td>
<td></td>
</tr>
<tr>
<td>NOS1</td>
<td>12q24.2-q24.31</td>
<td>Nitric oxide synthesis — cell-cell communication</td>
<td>3391C/T, 5266C/T</td>
</tr>
<tr>
<td>CMA1</td>
<td>14q12.2</td>
<td>Mast-cell chymotryptic serine protease</td>
<td>8s41XL, −1903G/A</td>
</tr>
<tr>
<td>IL4R</td>
<td>16p12.1-p12.2</td>
<td>α-chain of the IL-4 and IL-13 receptors</td>
<td>Il6E50Val, Glu551Arg</td>
</tr>
<tr>
<td>CCL11</td>
<td>17q21.1-q21.2</td>
<td>Epithelium-derived eosinophil chemoattractant</td>
<td>Ala23Thr, −1328G/A</td>
</tr>
<tr>
<td>CCL5</td>
<td>17q12.1-q12</td>
<td>Monocyte, T-cell and eosinophil chemoattractant</td>
<td>−403A/G, −28C/G</td>
</tr>
<tr>
<td>ACE</td>
<td>17q23.3</td>
<td>Inactivation of inflammatory mediators</td>
<td>In/del</td>
</tr>
<tr>
<td>TBX22R</td>
<td>19p13.3</td>
<td>Smooth-muscle contraction, inflammation</td>
<td>924T/C, 795T/C</td>
</tr>
<tr>
<td>TGFB1</td>
<td>19q13.1</td>
<td>Immunoregulation, cell proliferation</td>
<td>−509C/T</td>
</tr>
<tr>
<td>ADAM33</td>
<td>20p13</td>
<td>Cell-cell and cell-matrix interactions</td>
<td>Multiple SNPs</td>
</tr>
<tr>
<td>GSTT1</td>
<td>22q11.23</td>
<td>Environmental and oxidative stress — detoxification</td>
<td>A/null</td>
</tr>
</tbody>
</table>
Other Environment

- Tobacco smoke
- Diesel exhaust particles
- Chemical exposure
- Stress
- Maternal & other factors
Evaluating control and monitoring asthma
NHLBI Guidelines

- No updates to NHLBI Asthma Guidelines since 2007 (EPR-3)

- Many biologic therapies have been introduced recently

- New Guidelines should be here soon
Asthma Control

- **Impairment (Current)**
  - Minimal or no symptoms
  - Nocturnal
  - Minimal or no albuterol
  - No limitation activity
    - Exercise
  - Normal pulmonary function

- **Risk (Future)**
  - Exacerbations
    - Frequency & Severity
  - Minimal or no loss of lung function over time
  - Minimal or no adverse effects from medications

### NAEPP 3 Classification of Asthma Control

<table>
<thead>
<tr>
<th></th>
<th>Well controlled</th>
<th>Not Well controlled</th>
<th>Very Poorly controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>≤ 2 days/week</td>
<td>≥ 2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td><strong>Nighttime awakening</strong></td>
<td>≤ 2 X/month</td>
<td>1-3x/week</td>
<td>≥ 4x/week</td>
</tr>
<tr>
<td><strong>Interference with normal activity</strong></td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td><strong>Short acting bronchodilator use</strong></td>
<td>≤ 2 days/week</td>
<td>&gt; 2 days/\textbackslash\textbackslash week</td>
<td>Several times a day</td>
</tr>
<tr>
<td><strong>FEV\textsubscript{1} or PEF</strong></td>
<td>&gt; 80% predicted or personal best</td>
<td>60-80%</td>
<td>&lt; 60%</td>
</tr>
<tr>
<td><strong>Validated QOL Questionnaires</strong></td>
<td>Excellent</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>0-1/year</td>
<td>≥2 per/year</td>
<td>year</td>
</tr>
</tbody>
</table>

Evaluation & Monitoring

Clinical Tools
- Peak flow
- Spirometry
- FENO/Niox

Research Tools
- Exhaled breath condensate
  - Cooling exhaled air
  - Low pH, high H2O2
- Sputum eosinophils
  - Predict response to ICS
  - Exacerbations >2-3%
  - Difficult induce & analyze
- Urinary leukotrienes
- Periostin
- CT/MRI structural change
Spirometry

- Greatest absolute loss of lung function appears to occur very early in childhood
  - FEV$_1$ lower than cohort at every age
  - With increasing age, difference in FEV$_1$ larger
    - 18 years 530-mL male and 480-mL female

Taussig *J Allergy Clin Immunol.* 2003;111:661–675
Nitric Oxide

- **FENO**
  - Fractional nitric oxide concentration in exhaled breath

- **Objective measurement of eosinophilic airway inflammation**
  - Correlates with eosinophils in sputum, BAL, bronchial biopsy

- **Quantitative, noninvasive, safe & simple**

Interpreting FE\textsubscript{NO}

<table>
<thead>
<tr>
<th>Low FE\textsubscript{NO} Level</th>
<th>Intermediate/Increasing FE\textsubscript{NO} Level*</th>
<th>High FE\textsubscript{NO} Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 ppb in $\geq$12 years of age</td>
<td>25-50 ppb in $\geq$12 years of age</td>
<td>$&gt;$50 ppb in $\geq$12 years of age</td>
</tr>
<tr>
<td>&lt;20 ppb in &lt;12 years of age</td>
<td>20-35 ppb in &lt;12 years of age</td>
<td>$&gt;$35 ppb in &lt;12 years of age</td>
</tr>
</tbody>
</table>

- Eosinophilic inflammation less likely

- Symptomatic\textsuperscript{†} patients unlikely to benefit from ICS therapy; consider other possible etiologies$^\ddagger$

- Cautious interpretation; based on clinical judgment, consider initiating ICS therapy and monitor change in FE\textsubscript{NO} levels

- Symptomatic patients likely to benefit from ICS therapy; investigate allergen exposure

\textsuperscript{http://www.niox.com/en-US/feno-asthma/interpreting-feno/}
Exhaled Nitric Oxide (FENO)

- **Diagnosis and management of children**
  - Differentiate young children with asthma from those without\(^1\)
  - Identify children who are likely to respond to ICSs\(^2\)
  - Predict those children who will experience an asthma relapse after reduction of ICSs\(^3\)
  - Persistent and/or high allergen exposure as a factor associated with higher levels of FENO\(^4\)

---

1 Malmberg *Thorax*. 2003;58:494–499
2 Zeiger *J Allergy Clin Immunol*. 2006;117:45–52
3 Zacharasiewicz *Am J Respir Crit Care Med*. 2005;171:1077–1082
FENO & Exacerbations

- Fewer asthma exacerbations were registered in the FeNO group
  - 24% of the children in the FeNO group experienced one or more exacerbations per year
  - 48% in the clinical group (P = 0.017).

Peirsman et al. Pediatr Pulmonol. 2013 Sep 4
The role of allergies in asthma
Asthma and Allergies

- About 70% of asthmatics also have allergies\(^1\)
- Inhaled allergens role in Asthma\(^2\)
  - Development
  - Persistence
  - Severity
- Treat co-morbid allergic rhinitis
  - To improve asthma control\(^3\)

2. NAEPP EPR3 Guidelines for Management of Asthma (2007) NIH, NHLBI.
3. Guerra et al. 2002; Leynaert et al. 1999; Linneberg et al. 2002
FIGURE 4–1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: SABA PRN
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Low-dose ICS
Alternative: Either: Low-dose ICS + either LABA, LTRA, or Theophylline OR Medium-dose ICS

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: High-dose ICS + either LTRA or Theophylline

Step 4
Preferred: High-dose ICS + LABA
Alternative: High-dose ICS + either LTRA or Theophylline

Step 5
Preferred: High-dose ICS + LABA + oral systemic corticosteroid
Alternative: High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

Step 6
Step up if needed
(first, check adherence, inhaler technique, environmental control, and comorbid conditions)
Assess control
Step down if possible (and asthma is well controlled at least 6 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for Acute Symptoms:
SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Allergen Reduction

- Guidelines emphasize
  - Allergy testing to assess sensitivity to allergens
  - Multiple approaches to limit exposure to allergens
    - Especially dust mite, pets, & alternaria
  - Consider immunotherapy
Which medication to select?

**FIGURE 4-1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5-11 YEARS OF AGE**

- **Intermittent Asthma**
  - Consult with asthma specialist if step 4 care or higher is required.
  - Consider consultation at step 3.

- **Step 1**
  - Preferred: SABA PRN
  - Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

- **Step 2**
  - Preferred: Low-dose ICS
  - Alternative: Either: Low-dose ICS + either LABA, LTRA, or Theophylline OR Medium-dose ICS

- **Step 3**
  - Preferred: Medium-dose ICS + LABA
  - Alternative: Either: Medium-dose ICS + either LTRA or Theophylline

- **Step 4**
  - Preferred: High-dose ICS + LABA
  - Alternative: High-dose ICS + either LTRA or Theophylline

- **Step 5**
  - Preferred: High-dose ICS + oral systemic corticosteroid
  - Alternative: High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid

- **Step 6**
  - Step up if needed (first, check adherence, inhaler technique, environmental control, and comorbid conditions)
  - Assess control
  - Step down if possible (and asthma is well controlled at least 3 months)

**Each step:** Patient education, environmental control, and management of comorbidities.

**Steps 2-4:** Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Treatment

- **BADGER study**
- Best Add-on Therapy Giving Effective Responses (BADGER) trial
  - 182 children (6-17 years)
  - Uncontrolled asthma while receiving 100 μg of fluticasone twice daily
  - blinded step-up therapies in random order for 16 weeks
    - 250 μg of fluticasone twice daily (ICS step-up)
    - 100 μg of fluticasone plus 50 μg of a long-acting betaagonist twice daily (LABA step-up)
    - 100 μg of fluticasone twice daily plus 5 or 10 mg of a leukotriene-receptor antagonist daily (LTRA step-up)
BADGER

- LABA step-up therapy was most likely to be the best response

- Measured
  - asthma exacerbations
  - asthma-control days
  - forced expiratory volume in 1 second
Long Acting Beta Agonist (LABA)

- Combo ICS/LABA preferred step up for moderate to severe asthma uncontrolled on ICS alone
- Previously black box warning
  - Concern severe exacerbation and death
  - Removed in 2017 by FDA
- Transition to ICS alone once controlled
Anticholinergic Tiotropium

- Approved >6 yo
- Moderate asthma using ICS (with or without LTRA) without LABA
- Improved FEV1 and peak flow
Immunomodulation to help asthma
What is Allergen Immunotherapy (IT)?

- Repetitive administration of specific allergen(s)
- Patients with defined IgE-mediated sensitivity
- Develop immune tolerance upon re-exposure to those allergen(s)
Th1 vs Th2

Shift $T_H^2$ to $T_H^1$ CD4+ lymphocytes
Increase $T_H^1$ (IL-10 & IL-12) & IFN g
Decrease $T_H^2$ (IL-4, 5, & 13)
Increase Treg (CD4+CD25+)
IL-10 suppresses $T_H^2$ immune response
TGFb decreases $T_H^2$ response
Cochrane Review of SQ Immunotherapy

- 75 studies
- 3,188 asthma patients
- Subcutaneous Immunotherapy (SCIT) for DM, animal, pollen, mold & multiple allergens

Cochrane Review for SQ Immunotherapy

- Significant reduction
  - Asthma sx
  - Asthma medication
  - Allergen specific bronchial hyper-reactivity
  - Some reduction in non-specific bronchial hyper-reactivity
- No consistent effect on lung function
- 1 trial - benefit comparable to inhaled steroids

Decrease Development of Asthma

- Pollen immunotherapy in school-aged children
  - Only allergic rhinitis at the start
  - Reduce significantly the subsequent risk of the development of airway hyperresponsiveness and asthma

Biologic Therapy

- Omalizumab
- Benralizumab
- Mepolizumab
- Reslizumab
- Dupilumab
Role of Anti-IgE Treatment (Omalizumab) in Asthma
Cochrane Review of Anti-IgE

- 3143 subjects
- Mild to severe allergic asthma
- 14 studies
  - Randomized Controlled
  - Positive skin test and IgE level
  - Included mainly adult and adolescents
    - Some Children
    - Co-existing condition AR

Vignola et al Allergy 2004; 59: 709-17.
Cochrane Results for Omalizumab

- Small, but Significant Reduction in ICS
- Less Asthma Exacerbation
- Reduction in IgE Level 89-99%
- Placebo Effect Notable
FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

**Step 1**
- **Preferred:** SABA PRN
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 2**
- **Preferred:** Low-dose ICS + LABA
- **Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 3**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 4**
- **Preferred:** High-dose ICS + LABA
- **Alternative:** Consider Omalizumab for patients who have allergies

**Step 5**
- **Preferred:** High-dose ICS + LABA + oral corticosteroid
- **Alternative:** Consider Omalizumab for patients who have allergies

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Indications

- Moderate to severe persistent asthma
- Sx inadequately controlled on ICS
- Positive skin test or in vitro reactivity to a perennial aeroallergen
- IgE level between 30-700 IU

Limitations:
- Not for other allergic conditions, except urticaria
- Not for age <6 yo
- Not for acute bronchospasm
- Dose limitation based on weight 30-150 kg
Predictors of Response

- **Pooled analysis 2 DBPCCR**
  - Hx of emergency asthma tx in past year
    - Most predictive (p=0.015)
    - Defined: hospital, ER or urgent doctor visit
  - High ICS BDP >800 μg/d
  - Low FEV$_1$<65%
  - NOT predictive: Baseline IgE level

Bousquet et al, CHEST 2004; 125: 1378-86.
Asthma Medication Side Effect Concerns
Asthma Medication Side Effect Concerns

- Inhaled corticosteroids
- Leukotriene Receptor Antagonist (LTRA ie Montelukast)
Inhaled Corticosteroids

- Potential risks are well balanced by benefits\(^1\)
- High doses of ICS administered for prolonged periods of time (ie >1 year) & if in combination with frequent systemic steroids may
  - Adverse growth effects
  - Risk of posterior subcapsular cataracts
  - Reduced bone density

1 www.nhlbi.nih.gov/guidelines/asthma
Growth in CAMP study

- **Childhood Asthma Management Program**
  - Enrolled 5-13 years of age
  - Randomly assigned to receive 400 μg of budesonide, 16 mg of nedocromil, or placebo daily for 4 to 6 years

- Initial decrease in height associated with ICS in prepubertal children persisted as a reduction in adult height

- Decrease was NOT progressive or cumulative
  - Mean adult height was 1.2 cm lower (95% confidence interval [CI], −1.9 to −0.5) in the budesonide group than in the placebo group (P=0.001) and was 0.2 cm lower (95% CI, −0.9 to 0.5) in the nedocromil group than in the placebo group (P=0.61)
  - During the first 2 years, decreased growth velocity in the budesonide group occurred primarily in prepubertal participants

Growth & ICS

Figure 2. Effect of Budesonide on Adult Height.

Budesonide vs. Placebo Height Difference (cm)

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide vs. Placebo</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Mean Age (yr)

- Budesonide: 9, 11, 13, 25
- Placebo: 311, 296, 281, 281

No. of Participants

- Budesonide: 311, 296, 281, 281
- Placebo: 418, 396, 383, 377

LTRA and Suicide

- Phillip et al
  - Retrospective review of studies, no increased risk

- Schumock et al
  - Use of these medications NOT associated with increased risk of suicidal attempts in children and adolescents

- Further studies needed

Questions

- Contact information:
  - Jennifer DeMore, MD
  - (734) 434-3007
  - www.AnnArborAllergy.com