December 6, 2010

Pediatric Severe Asthma

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“Try this—I just bought a hundred shares.”
Disclosure Statement
Lanny J. Rosenwasser, MD

• RESEARCH STUDIES
  – Alcon, A-Z, GlaxoSmithKline, MBBH/MacArthur Foundation, National Institutes of Health

• CONSULTANT
  – Abbott Corp, Alcon, Alexion, Altana Pharmaceuticals, A-Z, Biogen Idec Corp, Genentech, GlaxoSmithKline, Merck, Novartis, Sanofi-Aventis

• SPEAKERS’ BUREAU
  – Alcon, Banyu Pharmaceuticals, Genentech,
  – Merck, Novartis
Characteristics of Asthma

- Narrowing of the airways
- Airway obstruction
- Airway inflammation
- Increased airway responsiveness

Immunohistopathologic Features of Asthma

- Denudation of airway epithelium
- Collagen deposition beneath basement membrane
- Edema
- Mast cell activation
- Inflammatory cell infiltration
  - Neutrophils
  - Eosinophils
  - Lymphocytes (TH-2 like cells)

Airway Remodeling

- Airway Wall Thickening
- Subepithelial Fibrosis
- Increased Myocyte Mass
- Myofibroblast Hyperplasia
- Mucous Metaplasia
Airway Remodeling: Physiologic Consequences

- Irreversible/Partially Reversible Airway Obstruction
- Airway Hyper-responsiveness
- Greater Decline in FEV1 than Controls (38ml/yr vs. 22ml/yr)
The importance of eosinophilic infiltration in airway inflammation

- Dendritic cell
  - IL-4, IL-13

- Th-2 cell
  - IL-9, IL-4
  - IL-3, IL-5
  - GM-CSF

- Mast cell
  - IL-3

- Basophil
- Eosinophil
  - Eotaxin

- Mucous
- Smooth muscle
- Blood vessels
- (Myo) fibroblasts
  - TGF-b
  - ET-1
  - VEGF

Th-2 inflammation
The epithelial-mesenchymal trophic unit
CD4 subsets: generation and function

Th1 cells (IFN-γ)
- Host defense: many microbes
- Systemic and organ-specific autoimmune diseases

Th2 cells (IL-4, IL-5)
- Host defense: helminths
- Allergic diseases

Th17 cells (IL-17)
- Host defense: fungi, bacteria
- Organ-specific autoimmune diseases

Regulatory T cells

Naïve CD4 T cell
- IFN-γ, IL-12, T-bet, Stat4
- IL-4, GATA3, Stat6
- TGF-β, IL-2, Foxp3, Stat5
- RORγt, Stat3
CD4⁺, CD25⁺ T lymphocytes

- Regulatory
- Express TGFβ, IL-10
- Suppressive to other T cells
- Express Foxp3 transcription factor
- IL-34, IL-35 growth factors
Complexity of Asthma

- Several orders of magnitude more complex
- Proteome, Transcriptome, Genome
- Tissues, Organs, Whole Body, Brain
- Third and Fourth Dimensions
Background

• First Asthma Guidelines 1991
  - Airway inflammation was central feature of asthma
  - Characteristics of asthma severity described
  - Asthma treatment based on disease severity
  - Proposed outcomes to be achieved
Stepwise Approach for Managing Asthma in Patients Aged ≥12

### Intermittent Asthma

- **Step 1**
  - **Preferred:** Low-dose ICS (A) + LABA (A)
  - **Alternative:** Cromolyn (A), LTRA (A), Nedocromil (A), or Theophylline (B)

- **Step 2**
  - **Preferred:** Low-dose ICS + LABA (A)
  - **Alternative:** Medium-dose ICS + LABA (A)

- **Step 3**
  - **Preferred:** Medium-dose ICS + LABA (B)
  - **Alternative:** High-dose ICS + LABA (B)

- **Step 4**
  - **Preferred:** High-dose ICS + LABA (B)
  - **Alternative:** Consider Omalizumab for Patients Who Have Allergies (B)

- **Step 5**
  - **Preferred:** High-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)

- **Step 6**
  - **Preferred:** High-dose ICS + LABA + Oral Corticosteroid AND Consider Omalizumab for Patients Who Have Allergies

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### Persistent Asthma: Daily Medication

- Consult with asthma specialist if Step 4 care or higher is required.
- Consider consultation at Step 3.

Each Step: Patient education, environmental control, and management of comorbidities

Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

**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 systemic oral 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.**

ICS = inhaled corticosteroids; LABA = long-acting β₂-agonist; LTRA = leukotriene receptor antagonist.

Antibodies to IgE (Anti IgE)

- Targets IgE, FcεRI
- Rhu Mab - E25 - Omalizumab, Xolair
- Reduces Free IgE (allergen specific)
- Reduces Eos (sputum, BAL, blood)
- Reduces FcεRI and FcεRII expression
- Efficacy - Asthma, AR
Major Changes in Long-Term Management

- Recommendations for three age groups presented separately
  - 0-4 years
  - 5-11 years
  - ≥ 12 years

- Expanded steps of therapy
  - 6 steps to simplify the action within each step
  - Medium dose ICS OR low dose ICS + LABA for patients not controlled on low dose ICS
  - Consider *omalizumab* for allergic patients not controlled on medium dose ICS + LABA
Definitions

**Severity**: the intrinsic intensity of the disease process, measured clinically in untreated patients or by the least amount of medicine required to achieve control.

**Control**: the degree to which the manifestations of asthma (symptoms, functional impairment, and risk of untoward events) are minimized and the goals of therapy are met.

**Responsiveness**: the ease with which control is achieved by therapy.
Domains of Severity and Control

• Impairment
  - Symptoms (day, night)
  - Reliever therapy
  - Activity
  - Lung function

• Risk
  - Exacerbation
  - Loss of lung function
  - Medication side effects
Steps of Therapy

• *Preferred* medications: Best balance of efficacy and safety in clinical trials for patients at that level of severity

• Must be tailored to individual patients’ needs, circumstances, and responsiveness
Principles of Step Therapy to Achieve Control

• Step up if not controlled
• If very poorly controlled, consider increase by 2 steps, oral corticosteroids, or both
• Before increasing pharmacologic therapy, consider as targets for therapy
  - Adverse environmental exposures
  - Poor adherence
  - Co-morbidities
DRAFT Asthma Guidelines

Stepwise approach to therapy - 3 age groups

- Youths ≥ 12 years and adults
- Children 5 to 11 years of age
- Children 0 to 4 years of age
Key Recommendations

Managing asthma in children 5-11 years

• Severity classification should guide initial therapy decisions.
• ICS are preferred initial long-term controller.
• Asthma control assessment should guide therapy adjustments.
### ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE

#### Components of Control

<table>
<thead>
<tr>
<th>Risk</th>
<th>Classification of Asthma Control (5–11 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td>Risk in lung growth</td>
<td>Evaluation requires long-term follow-up</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td></td>
</tr>
</tbody>
</table>

#### Recommended Action for Treatment

(See figure 4-1 for treatment steps)

- **Well Controlled**
  - Maintain current step
  - Regular follow-up every 3-6 months
  - Consider step down if well controlled for at least 3 months

- **Not Well Controlled**
  - Step up at least 1 step per month
  - Re-evaluate in 2-6 weeks
  - For side effects consider alternative treatment options

- **Very Poorly Controlled**
  - Consider short course of systemic corticosteroids
  - Step up 1-2 steps and
  - Re-evaluate in 2 weeks
  - For side effects consider alternative treatment options

Medication side effects can vary in intensity from none to very troublesome and worsen. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.
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.

Persistent Asthma: Daily Medication

Step 1
Preferred: SABA PRN

Step 2
Preferred: Medium-dose ICS
Alternative: Low-dose ICS
LTRA
Cromolyn, Nedocromil, or Theophylline

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

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

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

Step 6
Preferred: High-dose ICS + LABA + oral corticosteroid
Alternative: High-dose ICS + either LTRA or Theophylline + oral corticosteroid

AND Omalizumab may be considered for patients who have allergies

Assess control

Step up if needed (first, check adherence and environmental control and comorbid conditions)

Step down if possible (and asthma is well controlled at least 3 months)
Key Recommendations

Managing asthma in children 0-4 years

- Diagnosis is often difficult.
- Treatment has not been adequately studied.
- Criteria for initiation of long-term-control therapy:
  - 3 wheezing episodes in past year and positive asthma risk profile.
  - those who require symptomatic treatment > 2 days per week
  - two or more severe exacerbations within 6 months
<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (0-4 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td></td>
<td>≤2 days/week</td>
</tr>
<tr>
<td></td>
<td>1/month</td>
</tr>
<tr>
<td>Impairment</td>
<td>None</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td></td>
</tr>
</tbody>
</table>
STEPWISE APPROACH FOR MANAGING ASTHMA

**Intermittent Asthma**

Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.

**Step 1**

*Preferred:*
SABA PRN

*Alternative:*
Montelukast or Cromolyn

**Step 2**

*Preferred:*
Low-dose ICS

**Step 3**

*Preferred:*
Medium-dose ICS

**Step 4**

*Preferred:*
High-dose ICS

**Step 5**

*Preferred:*
High-dose ICS

**Step 6**

*Preferred:*
High-dose ICS

AND

Either: Montelukast or LABA

AND

Oral corticosteroids

Assess control

Step up if needed
(first, check adherence and environmental control)

Step down if possible
(and asthma is well controlled at least 3 months)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child &lt;5</td>
<td>Child 5–11</td>
<td>Child &lt;5</td>
</tr>
<tr>
<td>Beclomethasone HFA 40 or 80 mcg/puff</td>
<td>80–160 mcg</td>
<td>&gt;160–320 mcg</td>
<td>&gt;320 mcg</td>
</tr>
<tr>
<td>Budesonide DPI 200 mcg/inhalation</td>
<td>200–400 mcg</td>
<td>&gt;400–800 mcg</td>
<td>&gt;800 mcg</td>
</tr>
<tr>
<td>Inhalation suspension for nebulization (child dose)</td>
<td>0.25–0.5 mg</td>
<td>0.5 mg</td>
<td>0.5–1.0 mg</td>
</tr>
<tr>
<td>Flunisolide 250 mcg/puff</td>
<td>500–750 mcg</td>
<td>1,000–1,250 mcg</td>
<td>&gt;1,250 mcg</td>
</tr>
<tr>
<td>Flunisolide-HFA 80 mcg/puff</td>
<td>160 mcg</td>
<td>320 mcg</td>
<td>≥640 mcg</td>
</tr>
<tr>
<td>Fluticasone-HFA MDI: 44, 110, or 220 mcg/puff</td>
<td>176 mcg</td>
<td>88–176 mcg</td>
<td>176–352 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>100–200 mcg</td>
<td>200–400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
<tr>
<td>Mometasone DPI 200 mcg/inhalation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 mcg/puff</td>
<td>300–600 mcg</td>
<td>600–900 mcg</td>
<td>&gt;900 mcg</td>
</tr>
</tbody>
</table>

NA = not approved and no data available for children less than 12 years of age.
CONFOUNDERS OF ASTHMA

MODERATE  ←  SEVERE

STEP 3
- VCD
- SINUSITIS
- GERD

STEP 4
- VASCULITIS
- HES
- STEROID RESISTANCE
Poor Response to Medications

- Social Issues
- Patient Related
- Drug – Host Related
Poor Response to Medications

Social Issues:

• Barriers to care (lack of insurance)
• Complexity of Disease/Treatment
• Poor Provider Patient Interactions
• Breakdown in Patient Education
Poor Response to Medications

Patient Related:

• Non Compliance
• Psychological Problems (Depression)
• Poor Perception of Disease and Symptoms
Poor Response to Medications

Drug/Host Biologic Related:

- Side Effects
- Lack of Benefit
- Cost
- Lack of Biomarkers
- Pharmacokinetics (poor absorption, frequent dosing)
- Pharmacogenetics
PHARMACOGENETICS

STUDIES IN VARIATION OF DRUG RESPONSE

• Population variations > individual variation

\[ V_g + V_{Eg} \]

• Repeatability \( r = \frac{V_g + V_{Eg}}{V_P} \)
Pharmacogenetics
Pathways of Asthma Treatment

Arachidonate Metabolism
ALOX 5
LTC 4 Synthase

Bronchodilation
B₂AR

Immune/Inflammatory
IL-4/IL-4R
IL-13/IL-13R
GCR
## FCER2 – Pleiotropic Effects

<table>
<thead>
<tr>
<th>FCER2</th>
<th>SNP</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G9782a12</td>
<td>[T/G]</td>
</tr>
<tr>
<td></td>
<td>G9782a19</td>
<td>[T/C]</td>
</tr>
<tr>
<td></td>
<td>G9782a26</td>
<td>[C/T]</td>
</tr>
<tr>
<td></td>
<td>G9782a5</td>
<td>[C/T]</td>
</tr>
<tr>
<td></td>
<td>G9782a8</td>
<td>[C/A]</td>
</tr>
</tbody>
</table>

### Forest Haplotype Phenotype

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Phenotype</th>
<th>Frequency</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTCCC</td>
<td>BD % Change</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>TCTCA</td>
<td>BD Extremes</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>GTCTA</td>
<td>Steroid Extremes</td>
<td>0.13</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### CAMP Haplotype Phenotype

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Phenotype</th>
<th>Frequency</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTCTA</td>
<td>BD % Change</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>GTCTA</td>
<td>BD % Change 1 yr</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>GTCTA</td>
<td>BD % Change 4 yr</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>TCTTA</td>
<td>Steroid % Ch. 1 yr</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>TTCCC</td>
<td>Steroid % Ch. 4 yr</td>
<td>0.07</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Global P value for Steroid % Change 1 yr = 0.001
FCER2 – GCTTA Haplotype

- Hospitalizations: p = 0.0001 (Hosp) and 0.01 (ER)
- ER Visits: p = 0.0001 (Hosp) and 0.01 (ER)
IMMUNOMODULATORS

• Closer to Pathogenesis
• Disease Altering and Modifying
• Wave of the future
• Cost effectiveness will progress
• Can be applied to Immunotherapy
## Cytokine Modulation: Therapeutic Implications in Asthma

<table>
<thead>
<tr>
<th>Cytokine/Cytokine Antagonist</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor Antagonists:</strong></td>
<td></td>
</tr>
<tr>
<td>Interleukin 1 Receptor Antagonist</td>
<td>Inhibition of cytokine-mediated signal transduction</td>
</tr>
<tr>
<td>Soluble Interleukin-4 Receptor</td>
<td></td>
</tr>
<tr>
<td>Soluble Interleukin-1 receptor</td>
<td></td>
</tr>
<tr>
<td><strong>Antibodies:</strong></td>
<td></td>
</tr>
<tr>
<td>Humanized Anti-IL-5-Antibodies</td>
<td>Cytokine Inactivation</td>
</tr>
<tr>
<td>Humanized Anti-TNF Antibodies</td>
<td></td>
</tr>
<tr>
<td><strong>Cytokines with Anti-allergic inflammatory activities:</strong></td>
<td></td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Il-4 Antagonist</td>
</tr>
<tr>
<td>Interleukin-12</td>
<td>TH1-like lymphocyte differentiation</td>
</tr>
<tr>
<td>Interleukin-10, TGF-β</td>
<td>Anti-inflammatory cytokines</td>
</tr>
<tr>
<td>Study</td>
<td>Patients, No.</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
</tr>
<tr>
<td>Borish et al²⁰</td>
<td>25</td>
</tr>
<tr>
<td>Borish et al²⁰</td>
<td>62</td>
</tr>
<tr>
<td>Leckie et al²¹</td>
<td>24</td>
</tr>
<tr>
<td>Kips et al²⁶</td>
<td>26</td>
</tr>
<tr>
<td>Flood-Page et al³⁵</td>
<td>24</td>
</tr>
<tr>
<td>Howarth et al²⁷</td>
<td>17</td>
</tr>
<tr>
<td>Berry et al²⁴</td>
<td>10</td>
</tr>
</tbody>
</table>

*ICS = inhaled corticosteroid; OCS = oral corticosteroid; LABA = long-acting β₂-agonist; DB = double blind; R = randomized; Pl = placebo controlled; CO = crossover; EAR = early asthmatic response; LAR = late asthmatic response; eos = eosinophils; QOL = quality of life; FeNO = fractional exhaled nitrous oxide.
Key Central Role of IL-5 in Asthma
**IL-5 pathway inhibition in the treatment of asthma and Churg-Strauss syndrome**

**TABLE I. Promising anti-IL-5 drugs, anti-IL-5Rα drugs, or both**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mode of action</th>
<th>Recent results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Neutralizing</td>
<td>Steroid sparing and reduction of exacerbations in eosinophilic asthma; steroid sparing in patients with CSS and HES</td>
<td>1-4, 8, 9</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Neutralizing</td>
<td>Steroid sparing and reduction of exacerbations</td>
<td>9</td>
</tr>
<tr>
<td>MEDI-563</td>
<td>IL-5Rα</td>
<td>Cytotoxic and neutralizing</td>
<td>Reduction of eosinophilia</td>
<td>6, 7</td>
</tr>
</tbody>
</table>

*HES, Hypereosinophilic syndrome.*

**FIG 1.** Eosinophil count and prednisone dosage before and during mepolizumab treatment. **Black arrows** represent monthly pulses of cyclophosphamide, 1 g intravenous. **Gray arrows** represent infusion of mepolizumab, 750 mg intravenous. *M,* Months.
Ante-IL-5 in Human Asthma: Reduction in Exacerbations

- Severe (CCS-dependent) asthma
- Sputum eosinophilia required for enrollment
- No improvement in FEV1, control, symptoms

Anti-IL-5 in Human Asthma:

Allergy - 2030

- Systems Biology Approach to Allergic Cascades
- Bio Therapeutics
- Pharmacogenetic Profiling
- Early Intervention
INTERLEUKINS! "I hope this works Doc"