Controversial Issues in the Management of Childhood Asthma: Insights from NIH Asthma Network Studies

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Learning Objectives

• To review recent studies that impact the approach to asthma therapy.
• To summarize key findings that differentiate treatment by age in children.
• To indicate methods to select therapy to optimize effect and minimize adverse effects.
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Glaxo Smith Kline Health Outcomes Program.
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Goal of Management</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960’s</td>
<td>Relieve bronchospasm</td>
<td>Epinephrine</td>
</tr>
<tr>
<td></td>
<td>Prevent bronchospasm</td>
<td>Albuterol, theophylline</td>
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<tr>
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<td>Prevent allergen induced bronchospasm</td>
<td>Cromolyn</td>
</tr>
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<td>1970’s</td>
<td>Relieve bronchospasm</td>
<td>Inhaled glucocorticoids</td>
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<tr>
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<td>Prevent bronchospasm</td>
<td>Leukotriene modifiers</td>
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<td>Prevent allergen induced bronchospasm</td>
<td>Long acting β-agonists</td>
</tr>
<tr>
<td></td>
<td>Prevent and resolve inflammation</td>
<td>Combination therapy</td>
</tr>
<tr>
<td>1980’s</td>
<td>Relieve bronchospasm</td>
<td>Anti-IgE</td>
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<td>Prevent bronchospasm</td>
<td>Biomarkers/Genetics;</td>
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<tr>
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<td>Prevent allergen induced bronchospasm</td>
<td>Immunomodulators?</td>
</tr>
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<td>1990’s</td>
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<td>Prevent and resolve inflammation</td>
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</tr>
<tr>
<td></td>
<td>Prevent and resolve inflammation</td>
<td></td>
</tr>
<tr>
<td>2000’s</td>
<td>Achieve asthma control</td>
<td></td>
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<td></td>
<td>Personalized medicine;</td>
<td></td>
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<tr>
<td></td>
<td>Early intervention</td>
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</tr>
<tr>
<td>2010’s</td>
<td>Achieve asthma control</td>
<td></td>
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<td></td>
<td>Personalized medicine;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early intervention</td>
<td></td>
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</table>
# THE CHANGING FACES OF HEALTH CARE

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Management Goals</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950’s</td>
<td>Relief of symptoms</td>
<td>Physician only</td>
</tr>
<tr>
<td>1960’s</td>
<td>Symptom management</td>
<td>Physician/secretary</td>
</tr>
<tr>
<td>1970’s</td>
<td>Symptom prevention</td>
<td>Physician/office staff</td>
</tr>
<tr>
<td>1990’s</td>
<td>Disease management</td>
<td>Multiple physicians</td>
</tr>
<tr>
<td>2000’s</td>
<td>Disease control</td>
<td>Multidisciplinary staff</td>
</tr>
<tr>
<td>2010’s</td>
<td>Disease prevention</td>
<td>Strategic Partners</td>
</tr>
</tbody>
</table>
Primary Goal of Therapy: Achieving and Maintaining Asthma Control

• Primary goal of asthma therapy is to enable a patient to achieve and maintain control over their asthma
  - Eliminate impairments including symptoms, functional limitations, poor quality of life, and other manifestations of asthma
  - Reduce risk of exacerbations, ED visits, and hospitalizations

• Treatment goals are identical for all levels of asthma severity

Pediatric Population

- NAEPP defined three age groups
  - 12 years and above
  - 5 to 11 years of age
  - Less than 5 years of age
- Treatment goals are identical for all age groups
- Treatment steps vary by age due to available studies and disease presentation.

### Assessing Asthma Control and Adjusting Therapy in Youths 12 Years of Age and Adults

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control ≥12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤ 2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤ 2 x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤ 2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt; 80% predicted/p. best</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td>0</td>
</tr>
<tr>
<td>ATAQ</td>
<td>≤ 0.75</td>
</tr>
<tr>
<td>ACQ</td>
<td>≥ 20</td>
</tr>
<tr>
<td>ACT</td>
<td></td>
</tr>
</tbody>
</table>

### Impairment

- **Exacerbations requiring oral systemic corticosteroids**: 0-1/year 2/year (see note)
- **Progressive loss of lung function**: Consider severity and interval since last exacerbation
- **Treatment-related adverse effects**: Medication side effects can vary in intensity from none to vary troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.

### Risk

- **Recommended Action for Treatment**
  - Maintain current step
  - Regular followups every 1-6 months to maintain control.
  - Consider step down if well controlled for at least 3 months.
  - Step up 1 step, and
  - Reevaluate in 2-6 weeks.
  - For side effects, consider alternative treatment options.
  - Consider short course of oral systemic corticosteroids,
  - Step up 1-2 steps, and
  - Reevaluate in 2 weeks.
  - For side effects, consider alternative treatment options.
Stepwise Approach for Managing Asthma in Youths >12 Years of Age and Adults

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

**Step 1**
Preferred: Low-dose ICS  
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

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

**Step 3**
Preferred: High-dose ICS + LABA  
and  
Consider Omalizumab for patients who have allergies

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

**Step 5**
Preferred: High-dose ICS + LABA + oral corticosteroid  
and  
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: in full document)

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 the SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
### Stepwise Approach for Managing Asthma in Children Aged 5–11 Years

#### Classification of Asthma Severity

<table>
<thead>
<tr>
<th></th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
</tr>
</tbody>
</table>

#### Intermittent Asthma

- **Step 1**: 
  - **Preferred**: low-dose ICS
  - **Alternative**: cromolyn, LTRA, nedocromil, or theophylline
  - **Preferred**: SABA prn

#### Persistent Asthma: Daily Medication

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

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
<th>Step 6</th>
</tr>
</thead>
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</tbody>
</table>

- **Preferred**: low-dose ICS + LABA, LTRA, or theophylline
- **Preferred**: medium-dose ICS + LABA
- **Preferred**: high-dose ICS + LABA
- **Preferred**: medium-dose ICS + LTRA or theophylline
- **Preferred**: high-dose ICS + either LTRA or theophylline
- **Preferred**: high-dose ICS + LABA
- **Alternative**: high-dose ICS + LTRA or theophylline + oral systemic corticosteroid

- **Preferred**: high-dose ICS + LABA + oral systemic corticosteroid
- **Alternative**: high-dose ICS + LTRA or theophylline + oral systemic corticosteroid

#### Patient Education and Environmental Control

- Step 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

#### Quick-Relief Medication for All Patients

- **NAEPP, NHLBI, NIH. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. August 2007.**
Approaches to Personalizing Asthma Management

- Biomarkers – Which ones? What application?
- Combination therapy – How soon? What type?
- Genetics/epigenetics – Are we there yet?
- Immunomodulators – benefit-risk?
EPR-3 Recommendations: Step-Up Therapy

**Preferred:**
Low-dose ICS

**Alternative:**
Either cromolyn, LTRA, nedocromil, or theophylline
CLIC Primary Outcome: 
**FEV$_1$ Response**

- **FEV$_1$ % Change with Mt**
  - Mt alone: n=6 (5%)
  - Both: n=22 (17%)
  - Neither: n=69 (55%)

- **FP alone**: n=29 (23%)

Concordance Correlation 0.55 (0.43, 0.65)

<table>
<thead>
<tr>
<th>Baseline Characteristic (Categorical)</th>
<th>FP</th>
<th>Mt</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1} &lt; 90% predicted (pre-BD)</td>
<td>4.16**</td>
<td>1.78</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC &lt; 0.80 (pre-BD)</td>
<td>4.26**</td>
<td>2.40*</td>
</tr>
<tr>
<td>Methacholine PC\textsubscript{20} ≤ 1 mg/ml</td>
<td>2.62*</td>
<td>1.17</td>
</tr>
<tr>
<td>eNO &gt; 25 ppb</td>
<td>2.75*</td>
<td>2.03</td>
</tr>
<tr>
<td>TEC &gt; 350 cells/mm\textsuperscript{3}</td>
<td>2.34*</td>
<td>1.62</td>
</tr>
<tr>
<td>Serum ECP &gt; 15 µg/L</td>
<td>2.78**</td>
<td>1.18</td>
</tr>
<tr>
<td>IgE &gt; 200 kU/L</td>
<td>2.86**</td>
<td>0.96</td>
</tr>
<tr>
<td>uLTE\textsubscript{4} &gt; 100 pg/mg</td>
<td>2.03</td>
<td>3.22*</td>
</tr>
<tr>
<td>Female</td>
<td>1.14</td>
<td>2.30</td>
</tr>
<tr>
<td>Minority</td>
<td>0.84</td>
<td>1.98</td>
</tr>
<tr>
<td>Age ≤ 10 years</td>
<td>0.64</td>
<td>2.50*</td>
</tr>
</tbody>
</table>

**p ≤ 0.01; *p ≤ 0.05

Greater response to fluticasone over montelukast for increased FEV$_1$ was associated with:

- Higher bronchodilator use
- Greater response to bronchodilator
- Higher exhaled nitric oxide
- Higher serum eosinophilic cationic protein
- Lower pre-bronchodilator FEV$_1$ percent predicted
- Lower FEV$_1$/FVC
- Lower methacholine PC$_{20}$

CLIC Conclusions

How does the asthma-related phenotype influence the choice of medication selected to improve pulmonary function?

- Children with lower pulmonary function or higher levels of markers associated with allergic inflammation should receive ICS therapy.

- Children without these indicators could receive a therapeutic trial of either ICS or LTRA.

Follow-up Study

Can we predict who would have a better response to montelukast over ICS?

- LTE₄/FE_NO ratios were associated with a greater response to montelukast than FP for FEV₁ and for asthma control days.

- Children with high LTE₄/FE_NO ratios were likely to be younger and female and exhibit lower levels of atopic markers and methacholine reactivity.

EPR-3 Recommendations: Step-Up Therapy

Preferred:
EITHER:
Low-dose ICS + either LABA, LTRA, or Theophylline
OR
Medium-dose ICS

Step 1
Step 2
Step 3
Step 4
Step 5
Step 6

Intermittent Asthma
Persistent Asthma
**BADGER Protocol: Overview**

Three Treatment Period, Double blind, 3 way cross-over

### Run-in Period
- **Run-in period on 1xICS to demonstrate lack of control**
- **Run-in Period 2-8 weeks**
  - 1xICS = fluticasone DPI 100 µg BID

### Randomization

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation Period</td>
<td>Evaluation Period</td>
<td>Evaluation Period</td>
</tr>
<tr>
<td><strong>2.5 x ICS or</strong></td>
<td><strong>2.5 x ICS or</strong></td>
<td><strong>2.5 x ICS or</strong></td>
</tr>
<tr>
<td>1xICS + LABA or</td>
<td>1xICS + LABA or</td>
<td>1xICS + LABA or</td>
</tr>
<tr>
<td>1 x ICS + LTRA</td>
<td>1 x ICS + LTRA</td>
<td>1 x ICS + LTRA</td>
</tr>
</tbody>
</table>

**16 weeks**

2.5 x ICS = fluticasone DPI 250 µg BID
1xICS+LABA = fluticasone/salmeterol DPI 100/50 BID
1xICS+LTRA = fluticasone DPI 100 µg BID + montelukast
**Primary Outcome:** Probability of **BEST** Response Based on Composite Outcome*

LABA step-up was more than 1.5 times as likely to produce the best response

BADGER Study: Conclusions

- Significant variability in treatment response was noted at the Step-3 level.
- LABA step-up therapy was more than 1.5 times as likely to produce the best response.
- Many children demonstrated a best response to either step-up ICS or LTRA.
- Several characteristics, such as baseline ACT®, eczema, and race could be useful in selecting medication treatment for best response.

Summary Points

• Inhaled corticosteroids are the preferred long-term controller therapy at Step 2 level.
• At Step 3 Level, LABA step-up therapy was more than 1.5 times as likely to produce the best response.
• LTRA are alternative choices for Step 2 long-term controller and supplementary Step 3.
• Variable response can occur at either Step 2 or Step 3 therapy and alternative treatments may be selected within each Step before stepping up therapy.
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
- Randomized, multicenter, double-blind, parallel group, placebo-controlled trial
- 285 two and three year olds at high-risk for asthma
- Fluticasone 44 µg/puff or placebo (2 puffs b.i.d.)
Episode-free Days During the Entire Study

Guilbert TW and CARE Network. NEJM 2006;354:1985-97. Copyright © [2006] Massachusetts Medical Society. All rights reserved.
Outcomes During Observation Phase

• No differences between groups seen for:
  – Number of exacerbations requiring systemic corticosteroid bursts
  – Unscheduled physician visits
  – Hospitalizations
  – Bronchodilator use
  – Montelukast use
  – Respiratory system impedance

• Average # of days of supplemental ICS use: 26% less in ICS group (p=0.007) during first 3 months

• There were no significant differences in adherence, completed visits, drop-outs, treatment failures or serious adverse events between study groups.
Time to Any Supplementary Asthma Controller Medication

- Months 0-12: p-value 0.02
- Months 0-24: p-value 0.01
- Months 0-36: p-value 0.34

Guilbert TW and CARE Network. NEJM 2006;354:1985-97. Copyright © [2006] Massachusetts Medical Society. All rights reserved.
### Characteristics Associated with EFD Response

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Percentage of EFDs</th>
<th>P-value (ICS vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICS Mean (95% CI)</td>
<td>Placebo Mean (95% CI)</td>
</tr>
<tr>
<td>Male</td>
<td>93 (92, 95)</td>
<td>86 (83, 89)</td>
</tr>
<tr>
<td>Female</td>
<td>92 (89, 94)</td>
<td>92 (89, 94)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>93 (91, 95)</td>
<td>84 (80, 88)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>92 (89, 94)</td>
<td>93 (91, 94)</td>
</tr>
<tr>
<td>Run-In EFD &lt;80%</td>
<td>92 (90, 94)</td>
<td>84 (79, 87)</td>
</tr>
<tr>
<td>Run-In EFD &gt;=80%</td>
<td>93 (91, 95)</td>
<td>93 (91, 95)</td>
</tr>
<tr>
<td>ED/Hospitalization History</td>
<td>95 (93, 96)</td>
<td>87 (83, 90)</td>
</tr>
<tr>
<td>No ED/Hospitalization History</td>
<td>90 (87, 92)</td>
<td>91 (89, 93)</td>
</tr>
<tr>
<td>≥1 Positive Aeroallergen Skin Test</td>
<td>93 (91, 94)</td>
<td>86 (83, 89)</td>
</tr>
<tr>
<td>Negative Aeroallergen Skin Test</td>
<td>93 (90, 95)</td>
<td>92 (89, 94)</td>
</tr>
</tbody>
</table>

A study evaluating the effects of episodic use of an inhaled corticosteroid or a leukotriene receptor antagonist on the frequency and severity of acute wheezing episodes in young children
Background

• Population of interest
  – Young children with intermittent wheezing and severe exacerbations

• Research questions
  – Does treatment with ICS or LTRA early in the course of acute respiratory tract illnesses increase the proportion of episode free days over a 12 month period compared to conventional therapy*?
  – Do these treatments modify the severity of the acute episodes?

*Conventional therapy - inhaled bronchodilator followed by the sequential addition of systemic corticosteroids
Inclusion Criteria

1. Age 12-59 months

2. Recurrent episodes ($\geq 2$) of wheezing in the context of a URI over the preceding 12 months
   - $\geq 1$ documented by a health care provider, and
   - 1 episode within the preceding 6 months

3. Either 2 episodes of (a), OR 2 episodes of (b), OR 1 episode of (a) AND 1 episode of (b) within the past 12 months:
   a) Urgent care visit for wheezing which required treatment with at least a bronchodilator
   b) Episode of wheezing which required treatment with oral corticosteroids
Study Overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide (Pulmicort Respules® - AstraZeneca)</td>
<td>1.0 mg twice daily</td>
<td>7 days</td>
</tr>
<tr>
<td>Montelukast (Singulair® - Merck)</td>
<td>4mg granules (12-23 month)</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td>4 mg chewable tablets (24-59 months)</td>
<td></td>
</tr>
<tr>
<td>Albuterol - MDI or Nebulization Solution</td>
<td>4 times daily, then as needed</td>
<td>2 days</td>
</tr>
<tr>
<td>(Proventil® – Schering)</td>
<td></td>
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</tbody>
</table>
Criteria for Starting Study Medications

- Identification by parental interview of the typical pattern of symptom progression from respiratory illness to chest symptoms for each child
- Development of an individualized action plan
- Continual education to reinforce recognition of this symptom pattern
- Initiation of a 7-day study treatment course at the onset of the identified symptom pattern
Severity of Symptoms During Acute Episodes

**Proportion with an Episode Day**

- **Montelukast**
- **Budesonide**
- **Conventional Therapy**

**Trouble Breathing Score**

- **Montelukast**
- **Budesonide**
- **Conventional Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Montelukast</th>
<th>Budesonide</th>
<th>Conventional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong></td>
<td>5.3</td>
<td>5.3</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>P-value vs.</strong></td>
<td>0.008</td>
<td>0.004</td>
<td>---</td>
</tr>
</tbody>
</table>

Ref. Bacharier and CARE Network, JACI 2008;122:1127
Summary – Effect of Treatment Over 12 Months in the Entire Study Group

• The addition of montelukast or budesonide at the early signs of RTI-associated symptoms did not differ significantly from albuterol alone in:
  – The proportion of EFDs (primary outcome)
  – Oral corticosteroid use, urgent care visits, hospitalizations (secondary outcomes)
  – Growth or adverse effects (thus, both treatment approaches were safe)
Pediatric Asthma: Early Intervention

- Variability in asthma control should be anticipated.
- Reasons for variability should be identified and addressed.
- Inhaled glucocorticoids are the preferred first line long-term control therapy.
- Inhaled glucocorticoids are effective in alleviating symptoms but do not alter the natural history of asthma.
- Alternative therapies merit investigation as potential interventions following early diagnosis of asthma.
Early Intervention

Where do we go from here?

• Intermittent ICS therapy?
• Prevent asthma exacerbations?
• Montelukast as initial therapy?
• Anti-IgE?
• SLIT?
• Other immunomodulator therapy?
Maintenance vs Intermittent Inhaled Steroids In Wheezing Toddlers (MIST) Trial

A trial in preschool children with recurrent wheezing, positive asthma predictive index and prior year severe wheezing exacerbation that compares the effect of maintenance low-dose ICS versus intermittent high-dose ICS at the onset of respiratory tract illnesses on the rate of exacerbations requiring systemic corticosteroids.
Rationale for MIST

• Exacerbations & utilization major challenges in recurrent wheezing toddlers especially the high-risk.
• Two potential ICS regimens for control in toddlers
  – Maintenance low-dose ICS (PEAK)
  – Intermittent high-dose ICS during RTI (AIMS)
• More evidence-based data needed in the treatment of recurrent wheezing toddlers.
• A direct comparative trial is needed between maintenance low-dose ICS and intermittent high-dose ICS during RTI to reduce exacerbations.
• Such a study should be directed at the high-risk recurrent wheezing toddler
Interference With Stages of Asthma Progression

- Post-Natal Genetics
- Environment

- Pre-Natal Genetics
- Exposure

Inception of Disease

- Prevent

Cure

Treatment

Established Disease

Window of Opportunity
Asthma Management

Individualized or “Personalized” Approach

• Utilize asthma characteristics, biomarkers, and genetics to “profile” asthma severity and prognosis.
• Select medications based on driving factors of disease presentation and predictors of response.
• Monitor response and assess reasons for treatment failure.
• Develop proactive approach and adjust therapy accordingly.
Possibilities to improve asthma control

- Improve process of asthma management to apply step-care approach
- Identify alternative biomarker for Step 3
- Assess “step-up” treatment strategies to improve control and reduce exacerbations
- Environment control measures
- Reduce impact of viral infection
- Immune-based therapy to reduce impact of allergen-induced inflammation.
Future Approaches to Improving Asthma Management

- Genetics
- Early intervention
- Immunomodulators
- Biomarkers
- Combination therapy