Emily DiMango, MD
Asthma II

Director
John Edsall/John Wood Asthma Center
Columbia University Medical Center

Figure 1
Asthma Prevalence, 1980-2000

* Gap between 1995-1996 and 1997 indicates a break in trend due to the redesign of the 1997 NHIS.
Asthma in the US

- 6% of the population (17 million)
- Most common cause of hospitalization among children
- Higher prevalence in some areas
- 5,000 deaths per year.
- Undertreated

Comparison of Asthma Hospitalization Rates in Children Aged 0-14 in the U.S., NYS and NYC, 1999

- US: 3.25
- NYS (not incl. NYC): 2.09
- NYC: 7.94

HP 2000 Goal: 2.25/1,000
Risk factors for development of asthma

- Family history
- Sensitization to common allergens
- Maternal smoking
- Obesity
- Western lifestyle

- ?? Diet, pollution
Protective associations

- Cat and dog exposure in early life (protects against all allergen sensitization)
- Exposure to farm animals in early life (endotoxin)
- Day care in first 6 months of life
- Multiple siblings

Ownby, et al. JAMA 2002
Braun-Fahrlander, et al. NEJM 2002

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**Percentage of Children with Asthma According to the Number of Older Siblings and the Age at Entry into Day Care**

**Table 1. Percentage of Children with Asthma According to the Number of Older Siblings and the Age at Entry into Day Care.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Children*</th>
<th>Asthma</th>
<th>Relative Risk (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of older siblings‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>405</td>
<td>21</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>385</td>
<td>19</td>
<td>0.9 (0.7–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>176</td>
<td>14</td>
<td>0.7 (0.5–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>≥3</td>
<td>69</td>
<td>13</td>
<td>0.6 (0.4–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at entry into day care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 mo</td>
<td>899</td>
<td>19</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>7–12 mo</td>
<td>28</td>
<td>18</td>
<td>0.9 (0.4–2.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Birth to 6 mo</td>
<td>69</td>
<td>9</td>
<td>0.4 (0.2–1.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Ball M NEJM 2000
Effect of Endotoxin exposure on wheeze

**Asthma Definition**

- Chronic inflammatory disorder of the airways
- Usually associated with atopy (extrinsic, intrinsic)
- Obstruction to airflow which is reversible (either spontaneously or with use of medications)
- Airway hyperresponsiveness and narrowing in response to a variety of stimuli
Asthma: A Lung Disease with Airway

- Obstruction (at least partially reversible)
- Hyperreactivity
- Inflammation

Normal Bronchiole

Asthma

Mast cells
Bronchospasm
Edema (and mucus)
Eosinophils
Lymphocytes

Busse, W, NEJM 2001; 344: 5
Airway Inflammatory Changes

Airway inflammation - Early and late Response

Triggers
Mast cells

Mediators
Leukotrienes
Histamine
Prostaglandins
Platelet activating factor
Enzymes
Cytokines

Lymphocytes
Eosinophils
 Diagnostic Criteria For Asthma

• Cough, dyspnea, wheeze, chest tightness
• Waxing and waning symptoms
• Heightened airway reactivity – exacerbations upon exposure to stimuli
• Episodic airflow limitation in response to antigenic triggers.
Physiologic features of asthma

• Reversible airflow limitation (obstructive defect) with a significant (>12%) change in FEV1 in response to inhaled bronchodilator.

• response to bronchoprovocation testing - challenge with agent (histamine, cold air) which provokes bronchial narrowing (decrease of 20% in FEV1) in sensitive individuals. (Clinical trials, professional athletes)
Methods For Measuring Airway Caliber
Asthma exacerbation

- Asthma trigger leads to bronchoconstriction and increase in airway inflammation–narrowing of airway lumen
- Increased resistance to airflow
- Reduction in FEV1, PEFR
- Will reverse either spontaneously (eventually) or with use of medication

Contributing Factors to Asthma Exacerbation

- Poorly controlled airway inflammation
- Cold air
- Exercise
- Upper respiratory tract infection
- sinusitis, rhinitis, GERD
- First or second hand tobacco smoke
- environmental allergens – indoor and outdoor
Asthma Triggers

Seasonal Patterns in Viral Infection and Asthma Exacerbation

Hospital Admissions 1989-1990

No. of Respiratory Infections in a Cohort of Schoolchildren

No. of Hospital Admissions for Asthma in Children (<20 y)

*In Wessex Regional Health Authority.
Gas exchange abnormalities in acute asthma exacerbation

- Low V/Q leads to hypoxemia
- Increased ventilatory drive leads to reduction in pCO2.
- As severity of airflow obstruction increases, respiratory muscle fatigue develops and pCO2 “pseudo-normalizes” then becomes elevated.

Physical Examination

Physical examination of the chest may be normal.

- Wheezing or prolonged force expiration
  - may not correlate with obstruction
- Hyperinflation of the lungs
- Use of accessory muscles
Pathologic targets in asthma

- Bronchial smooth muscle
- Airway inflammatory cells
- Inflammatory cytokines
- Bronchial epithelium
- Bronchial blood vessels (anti-VLA-4)

Reliever vs. controller medications

Reliever medications
- Short acting bronchodilators

Controller medications
- Inhaled corticosteroids
- Leukotriene modifiers
- Theophylline
- Cromolyn
- Long acting bronchodilators
**β₂-agonists (Albuterol)**

- Bind to β₂ receptors on airway smooth muscle cells, cause relaxation of muscle and bronchial dilatation
- Most effective bronchodilators available, short term relief of bronchoconstriction
- Rapid onset of activity; duration of action 3-6 hours.
- “rescue” therapy for symptom relief
- No effect on chronic inflammation

**Side effects of β₂ agonists**

- Due to non-airway β₂ activity: skeletal muscle tremor
- Due to overlap β₁ activity: tachycardia, arrhythmia, hypokalemia
- Excessive use related to higher mortality and morbidity – may be marker for more severe disease/airway inflammation
- Possible tachyphylaxis – mild downregulation of cell surface receptor number and desensitization of the receptor to drug – not clinically significant.
Effect of polymorphisms at the amino acid residue 16 locus of the B\textsubscript{2} adrenergic receptor

**Glucocorticoids (Steroids)**

- Most effective anti-inflammatory agent for treatment of persistent asthma
- Reduce influx of inflammatory cells into the airways (eosinophils, lymphs)
- Reduce production of pro-inflammatory cytokines by airway epithelial cells
- Reduce airway edema and mucus production
- May reduce airway remodeling
Inhaled glucocorticoids

- First line therapy for all but very mild asthma
- Early initiation of therapy may preserve lung function over long term

Side effects of inhaled steroids

- Thrush and dysphonia are local effects

- Potential systemic effects: growth retardation, adrenal suppression, osteoporosis, cataracts, acne, skin fragility with high doses.
Early initiation of inhaled corticosteroids preserves lung function

Leukotrienes in Asthma

- Chemoattractant for eosinophils
- Smooth muscle contraction
- Vascular permeability
- Enhanced mucus production
- Can block by leukotriene synthesis inhibitors or receptor antagonists (oral agents)
Long acting beta agonists

- Inhaled salmeterol (component of Advair®) and formoterol
- Duration of action 12 hours, bid drug
- Delayed onset of action (30 minutes)
- Efficacious in moderate to severe asthma
- Allow reduction of inhaled steroid dose
- **Not monotherapy**; ie use only as add on therapy to anti inflammatory agents – avoid masking of inflammation

- New black box warning: Increased mortality and serious events in some patients taking long acting beta agonists, particularly African Americans
Effect of Salmeterol added to low dose inhaled steroids

Mean Change in FEV$_1$ from Baseline (L)

- Salmeterol + BDP 168
- BDP 336

*P ≤ 0.05 vs BDP 336 mcg
*P ≤ 0.001 vs baseline
Baseline FEV$_1$
Salmeterol + BDP 168 = 2.30 L
BDP 336 = 2.31 L

Adapted from J. Murray, Allergy and Asthma Proc. 1999;20:173-180.

Occurrence of asthma-related deaths by phase and study year

**Anticholinergic Drugs**
*(Ipratropium Bromide)*

- Block muscarinic receptors on airway smooth muscle
- Inhibit bronchoconstriction caused by cholinergic nerves, no action against the direct effects of mediators on airway smooth muscle
- Slower onset of action; reduced efficacy compared with $b_2$ agonists
- Additive when used in combination with $b_2$ agonists

**theophylline**

- Phosphodiesterase inhibitor – increases intracellular cAMP in inflammatory cells
- Anti-inflammatory and bronchodilator properties
- Additive therapy when not adequately controlled with inhaled steroids
- Therapeutic ratio limits use; better agents available; more selective agents under study
Biologics in treatment of asthma

• Targeted toward specific mediators
• Anti-IL5 tested, not efficacious
• Monoclonal Ab-IgE is first compound commercially available.
• Expensive

Monoclonal Ab – IgE (omalizumab, xolair®)

• Approved for treatment of moderate and severe asthma only in atopic asthma
• Effective in reducing asthma exacerbation rate and reducing required corticosteroid dose
• Subcutaneous injections 1-2x/month
Effect of anti-IgE on corticosteroid dose in severe asthmatics


Treatment of acute asthma exacerbation

- High dose $b_2$ agonist (inhaled, SQ, IV)
- Nebulized anticholinergics
- epinephrine
- Corticosteroids
- Oxygen
- Mechanical ventilation
Assessment of asthma severity during office visits

- Nocturnal awakenings from asthma symptoms
- Days per week with symptoms
- Need for rescue bronchodilators
- Activity limitation because of asthma
NAEPP (2002) Guidelines for Asthma Severity classification

- **Mild intermittent**: symptoms < 2x/week, nocturnal symptoms < 2x/month, normal FEV1
- **Mild persistent**: symptoms 3-6x/week, 3-4 awakenings/month, normal FEV1
- **Moderate persistent**: daily symptoms, >5 nocturnal awakenings/month, FEV1 60-80%
- **Severe persistent**: continual symptoms, FEV1 < 60%

Long term control of asthma

- **Symptoms occurring more than twice per week** is an indication for **daily anti-inflammatory therapy**.
- Step up anti-inflammatory therapy based on need for bronchodilators and frequency of symptoms
- Can use leukotriene modifiers and long acting b-agonist as steroid sparing agents.
Asthma which is difficult to control

- Observe inhaler technique
- Other diagnoses
- Adherence to regimen
- Reflux or sinusitis present
- Sensitivity to medication (NSAIDS, food additives)
- Abuse of OTC inhalers
- Environmental stimulus – mold, smoking

Future Goals

- Pharmacogenetics
- Identification of genes responsible for disease
- Biologics (monoclonal blocking antibodies)
- Th2/Th1 balance - vaccines
- Reduce racial disparities in asthma morbidity and mortality
No Limits
Play
Work
Live
Control Your Asthma
Reach New Heights
IN WASHINGTON HEIGHTS

Columbia University Asthma Coalition
[212] 305-0631