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

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

### 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</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of older siblings</td>
<td>0</td>
<td>405</td>
<td>21</td>
<td>1.0</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>160</td>
<td>19</td>
<td>0.9 (0.7-1.0)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>174</td>
<td>14</td>
<td>0.7 (0.5-1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<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>&gt;12 mo</td>
<td>809</td>
<td>19</td>
<td>1.0</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<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></td>
<td>Birth to 6 mo</td>
<td>69</td>
<td>9</td>
<td>0.6 (0.2-1.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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

Busse, W, NEJM 2001; 344: 5

Asthma: A Lung Disease with Airway 
- Obstruction (at least partially reversible)
- Hyperreactivity
- Inflammation

Mast cells
Bronchospasm
Edema
(and mucus)
Eosinophils
Lymphocytes

Normal Bronchiole
Asthma
Airway Inflammatory Changes

![Image of 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

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 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
Asthma Triggers

Seasonal Patterns in Viral Infection and Asthma Exacerbation

Hospital Admissions 1989-1990

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

No. of Respiratory Infections in a Cohort of Schoolchildren

* 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

<table>
<thead>
<tr>
<th>Reliever medications</th>
<th>Controller medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short acting bronchodilators</td>
<td>• Inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• Leukotriene modifiers</td>
</tr>
<tr>
<td></td>
<td>• Theophylline</td>
</tr>
<tr>
<td></td>
<td>• Cromolyn</td>
</tr>
<tr>
<td></td>
<td>• Long acting bronchodilators</td>
</tr>
</tbody>
</table>

**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.

**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.

**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


Occurrence of asthma-related deaths by phase and study year

Anticholinergic Drugs (Ipratropium Bromide)

- Block muscarinic receptors on airway smooth muscle
- Inhibit bronchoconstrictor caused by cholinergic nerves, no action against the direct effects of mediators on airway smooth muscle
- Slower onset of action; reduced efficacy compared with β₂ agonists
- Additive when used in combination with β₂ 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 β2 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