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

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

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

<table>
<thead>
<tr>
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<th>US</th>
<th>NYS (not incl. NYC)</th>
<th>NYC</th>
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<tbody>
<tr>
<td>Rate per 1,000 Population</td>
<td>2.25</td>
<td>2.09</td>
<td>7.94</td>
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Asthma Prevalence, 1980-2000

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


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Airway Inflammatory Changes

Viral Respiratory Infections

Hospital admissions for asthma correlate with virus isolation peaks and school terms.

Methods For Measuring Airway Caliber

Diagnostic Criteria For Asthma

- Cough, dyspnea, wheeze, chest tightness
- Waxing and waning symptoms
- Airway hyperresponsiveness (narrowing), to naturally occurring stimuli
- Heightened airway reactivity – exacerbations upon exposure to stimuli
- Episodic airflow limitation in response to antigenic triggers.
### Physiologic features of asthma
- Reversible airflow limitation with a significant (>12%) change in FEV1 in response to inhaled bronchodilator.
- Response to bronchoprovocation testing - challenge with agent which provokes bronchial narrowing (decrease of 20% in FEV1) in sensitive individuals.

### Asthma exacerbation
- Asthma trigger leads to increase in airway inflammation and bronchoconstriction – 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

### Gas exchange abnormalities in acute asthma exacerbation
- V/Q mismatch leads to hypoxemia
- Increased ventilatory drive leads to reduction in pCO2.
- As severity of airflow obstruction increases, pCO2 "pseudo-normalizes" then becomes elevated as respiratory muscle fatigue develops.
Hemodynamic changes during acute asthma

- Pulsus paradoxus correlates with level of airflow obstruction
- Cardiac output normal to increased
- RV strain with p-pulmonale on EKG

Reliever vs. controller medications

**Reliever medications**
- Short acting bronchodilators

**Controller medications**
- Inhaled corticosteroids
- Leukotriene modifiers
- Theophyllin
- Cromolyn
- Long acting bronchodilators

Pathologic targets in asthma

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

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
- Many different preparations with differences in systemic absorption due to first pass metabolism
Side effects of inhaled steroids

• Thrush and dysphonia are local effects
• Systemic effects: growth retardation, adrenal suppression, osteoporosis, cataracts, acne, skin fragility with high doses.
• Biochemical markers of systemic effects are present with use of high dose

Concerns regarding use of inhaled glucocorticoids

• Adrenal suppression
• Bone demineralization
• Cataracts
• Growth retardation in children
• Related to dose and duration of therapy
**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)

**Side effects of $\beta_2$ agonists**

- Due to non-airway $\beta_2$ activity: muscle tremor, metabolic
- Due to overlap $\beta$ activity: tachycardia, arrhythmia, hypokalemia
- Regular use related to higher mortality and morbidity – may be related to polymorphisms in $\beta_2$ receptor
- Possible tachyphylaxis – mild downregulation of cell surface receptor number and desensitization of the receptor to drug.

**$\beta_2$-agonists (Albuterol)**

- Bind to $\beta_2$ 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
- Regularly schedule vs. prn use

**Other potential explanations**

- Use of $\beta$-agonists is a marker of disease severity
- $\beta$-agonists have adverse effects on extra-pulmonary organ systems
- $\beta$-agonists may make asthma worse (by increasing airway hyperresponsiveness)
- Over reliance on $\beta$-agonists may mask severity of disease and delay use of additional modes of therapy to address underlying airway inflammation
### Long acting beta agonists

- Inhaled salmeterol and formoterol
- Duration of action 12 hours
- Delayed onset of action (30 minutes)
- Efficacious in moderate to severe asthma
- Useful for nocturnal asthma
- Not monotherapy; ie add on to anti-inflammatory therapy to reduce need for inhaled steroids
- Allow reduction of inhaled steroid dose
- **New black box warning:** Increased mortality and serious events in patients taking long acting beta agonists

### Cromyln agents for asthma (Intal, Nedocromil)

- Stabilize mast cells, reduce release of proinflammatory agents.
- Useful for exercise induced asthma, but not as effective as beta agonists
- Extremely safe

### 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

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**Occurrence of asthma-related deaths by phase and study year**

Exercise induced asthma (EIA)

- Occurs in 80-90% of patients with chronic asthma
- 30-40% of athletes with allergies
- 10% of healthy athletes without allergies or asthma
- 17% in Winter Olympic athletes, 16% in summer Olympics
- Vigorous physical activity with associated hyperventilation of cool, dry air triggers acute airway narrowing, classically at the end of exercise when airways rewarm and rehumidify
- Higher prevalence reported among athletes than in general healthy population

Biologics in treatment of asthma

- Anti-IL5 tested, not efficacious
- Anti-IgE is first compound commercially available.
- Expensive
- Subcutaneous injection
- ? Duration of therapy

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 over the past month.
- Days per week with symptoms
- Need for rescue bronchodilators
- Activity limitation because of asthma

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

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%

Future Goals

- Pharmacogenetics
- Identification of genes responsible for disease
- Biologics (monoclonal blocking antibodies)
- Th2/Th1 balance - vaccines
- Reduce morbidity and mortality in inner city minorities

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.