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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

<table>
<thead>
<tr>
<th></th>
<th>Rate per 1,000 Population</th>
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<tbody>
<tr>
<td>US</td>
<td>3.25</td>
</tr>
<tr>
<td>NYS (not incl. NYC)</td>
<td>2.09</td>
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<tr>
<td>NYC</td>
<td>7.94</td>
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HP 2000 Goal: 2.25/1,000
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

[Diagram: Normal Bronchiole vs. Asthma with cells labeled Mast cells, Bronchospasm, Edema (and mucus), Eosinophils, Lymphocytes]

Airway Inflammatory Changes
Asthma Triggers

Airway inflammation - Early and late Response

Triggers

Mast cells

Mediators

Leukotrienes
Histamine
Prostaglandins
Platelet activating factor
Enzymes
Cytokines

Lymphocytes

Eosinophils
Viral Respiratory Infections

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


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Early and Late Asthmatic Response Following Antigen Challenge

12-patient, 2-period crossover study

Early asthmatic response (EAR) and late asthmatic response (LAR)

FEV₁, Percent Change (mean ± SD)

Montelukast vs Placebo

Ear = early asthmatic response; LAR = late asthmatic response

Methods For Measuring Airway Caliber

- Maximum PEFR airflow achieved
- FVC, FEV, PEF 25%-75%
- Airway Resistance
- Home
- Office/Clinic
- Clinic/Laboratory

A

<table>
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<th>Liters</th>
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FEV = 4.0
FVC = 5.0
% = 80

FEV = 1.3
FVC = 3.1
% = 42

FVC = TLC - RV

B
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

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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

- 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
- Theophyllin
- Cromolyn
- Long acting bronchodilators
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
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)
**ß2-agonists (Albuterol)**

- Bind to ß2 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

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**Side effects of ß2 agonists**

- Due to non-airway ß2 activity: muscle tremor, metabolic
- Due to overlap ß1 activity: tachycardia, arrhythmia, hypokalemia
- Regular use related to higher mortality and morbidity – may be related to polymorphisms in ß2 receptor
- Possible tachyphylaxis – mild downregulation of cell surface receptor number and desensitization of the receptor to drug.
Effect of polymorphisms at the amino acid residue 16 locus of the B₂ adrenergic receptor

![Graph showing the effect of polymorphisms at the amino acid residue 16 locus of the B₂ adrenergic receptor.]

Other potential explanations

- Use of β-agonists is a marker of disease severity
- β-agonists have adverse effects on extra-pulmonary organ systems
- β-agonists may make asthma worse (by increasing airway hyperresponsiveness)
- Over reliance on β-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
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 $b_2$ agonist (inhaled, SQ, IV)
- Nebulized anticholinergics
- Epinephrine
- Corticosteroids
- Oxygen
- Mechanical ventilation
Assessment of asthma severity during office visits

- Nocturnal awakenings from asthma symptoms over the past month.
- 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 morbidity and mortality in inner city minorities