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Asthma II

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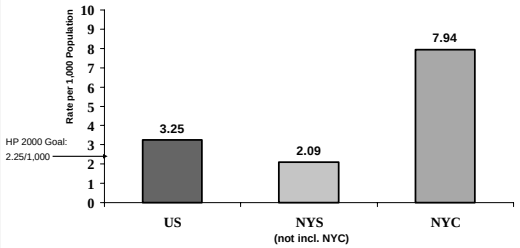
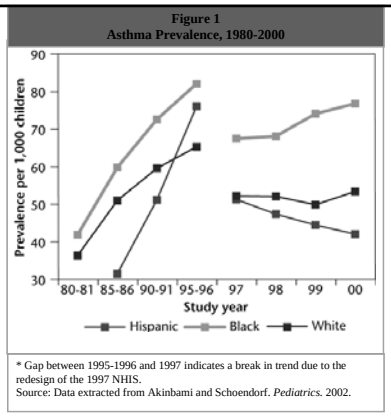
Comparison of Asthma Hospitalization Rates in Children Aged 0-14 in the U.S., NYS and NYC, 1999



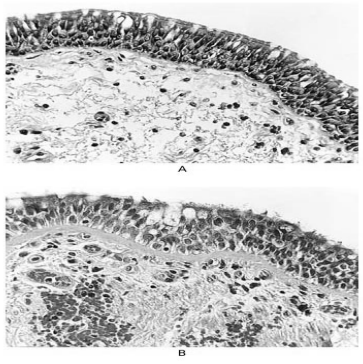


Asthma Definition

- 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 in the US

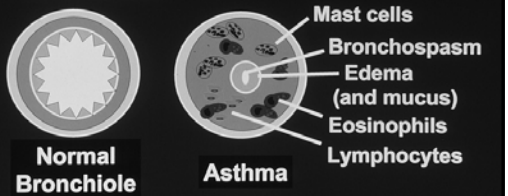
- 6% of the population (17 million)
- Most common cause of hospitalization among children
- Higher prevalence in some areas
- 5,000 deaths per year.
- Undertreated



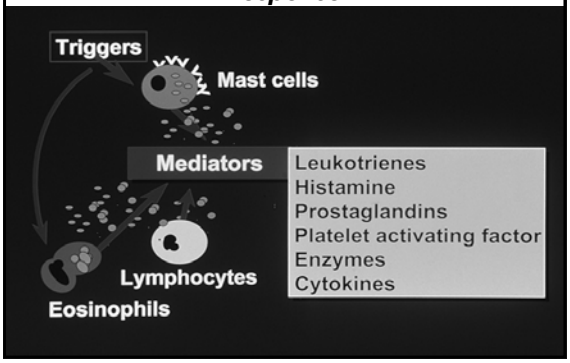
Busse, W, NEJM 2001; 344: 5

Asthma: A Lung Disease with Airway

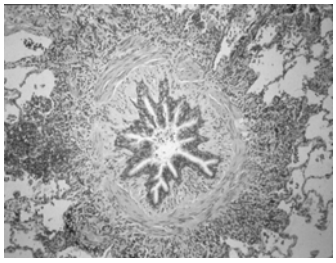
- Obstruction (at least partially reversible)
- Hyperreactivity
- Inflammation



Airway inflammation - Early and late Response

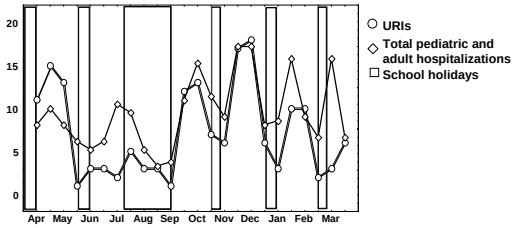


Airway Inflammatory Changes



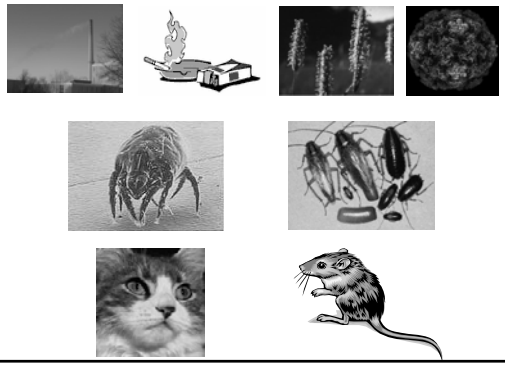
Viral Respiratory Infections

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



Adapted with permission from Johnston SL et al. *Am J Respir Crit Care Med.* 1996;154:654. Official Journal of the American Thoracic Society. ©American Lung Association.

Asthma Triggers



Methods For Measuring Airway Caliber

Diagnostic Criteria For Asthma

- Cough, dyspnea, wheeze, chest tightness
- Waxing and waning symptoms
- Airway hyperresponsiveness (narrowing), to naturally occuring 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, pCO_2 "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

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

Pathologic targets in asthma

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

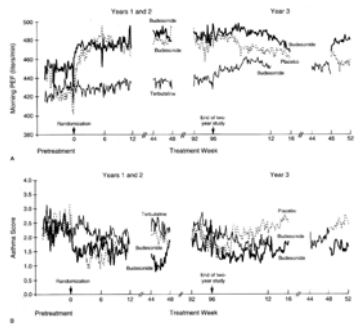
Inhaled glucocorticoids

- 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

Early initiation of inhaled corticosteroids preserves lung function



Haahtela, T. et al. N Engl J Med 1994;331:700-705

Concerns regarding use of inhaled glucocorticoids

- Adrenal suppression
- Bone demineralization
- Cataracts
- Growth retardation in children
- ?related to dose and duration of therapy

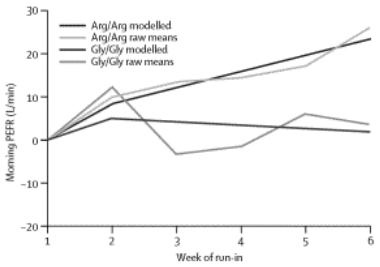
Leukotrienes in Asthma

- 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 b_2 agonists

- Due to non-airway b_2 activity: muscle tremor, metabolic
- Due to overlap b_1 activity: tachycardia, arrhythmia, hypokalemia
- Regular use related to higher mortality and morbidity – may be related to polymorphisms in b_2 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 B_2 adrenergic receptor



ß$_2$-agonists (Albuterol)

- Bind to ß$_2$ 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 b-agonists is a marker of disease severity
- b-agonists have adverse effects on extra-pulmonary organ systems
- b-agonists may make asthma worse (by increasing airway hyperresponsiveness)
- Over reliance on b-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**

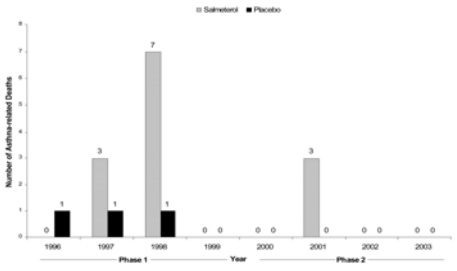
Cromyln agents for asthma (Intal, Nedocromil)

- 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 bronchoconstriciton caused by cholingeric 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

Occurrence of asthma-related deaths by phase and study year



Nelson, H. S. et al. Chest 2006;129:15-26

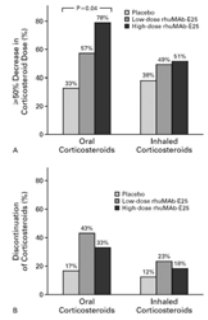
theophylline

- Phosphodiesterase inhibitor – increases intracellullar 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

Effect of anti-IgE on corticosteroid dose in severe asthmatics



Milgrom, H. et al. N Engl J Med 1999;341:1966-1973

Treatment of acute asthma exacerbation

- High dose b_2 agonist (inhaled, SQ, IV)
- Nebulized anticholinergics
- epinephrine
- Corticosteroids
- Oxygen
- Mechanical ventilation

Biologics in treatment of asthma

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

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
- Senistivity 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 frquency of symptoms
- Can use leukotriene modifiers and long acting b-agonist as steroid sparing agents.