Asthma

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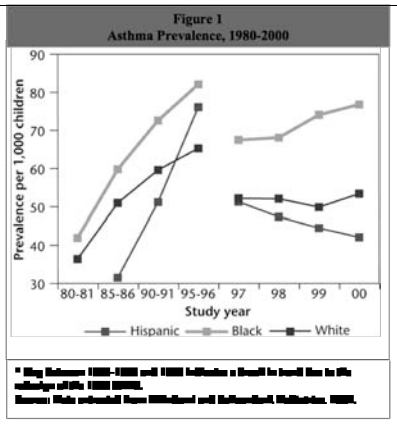
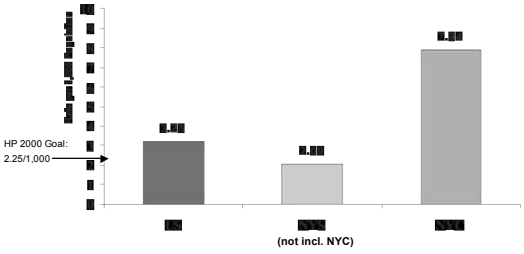
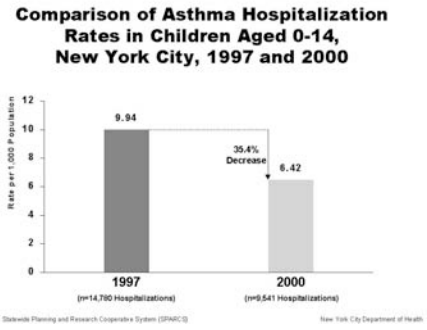


Asthma in the US

- 7% of the population (18 million)
- Most common cause of hospitalization among children
- Higher prevalence in some areas
- Prevalence doubled 1980-1998, now stable
- 3,700 deaths in 2004, down from peak of 5,700 in 1996

Comparison of asthma hospitalization rates in children aged 0-14 in the US, NYS and NYC, 1999

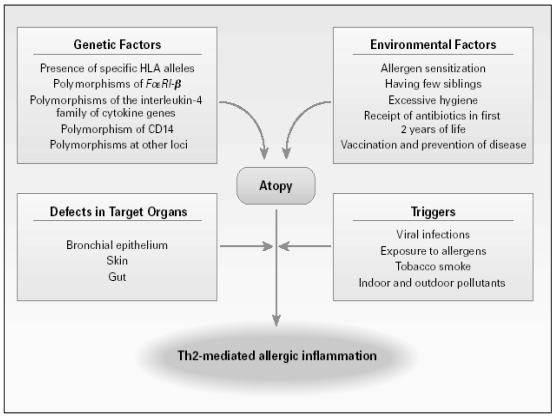




Risk factors

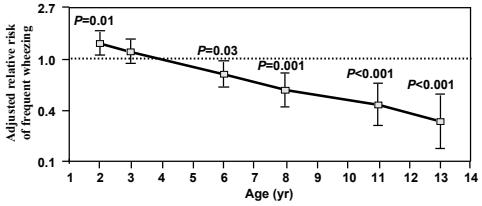
- Family history (genetics)
- Sensitization to common allergens
- Maternal smoking
- Obesity
- Western lifestyle

- Diet?
- Pollution-assoc with exac vs new incidence?

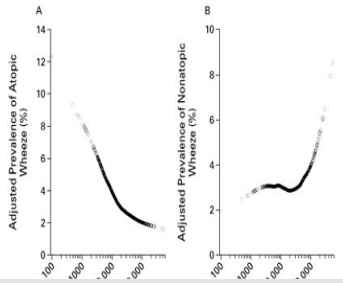


Protective effect of day care in infancy and older siblings

Children who had ≥2 older siblings or attended day care during first 6 mo of life had increased risk of wheeze early in life but decreased risk later.



Effect of endotoxin exposure on wheeze

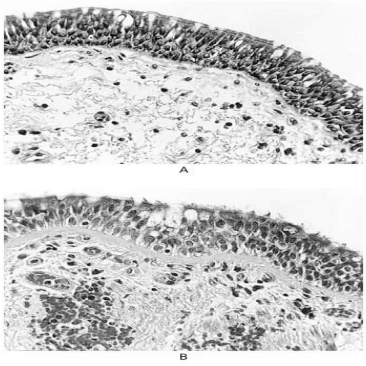


Endotoxin in mattress

Braun-Fahrlander, C. et al. N Engl J Med 2002;347:869-87

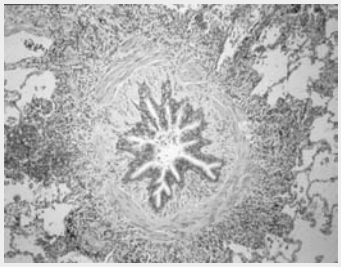
Asthma definition

- 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

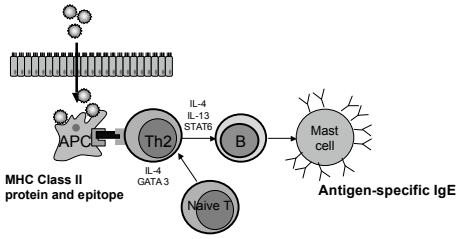


Busse, W, NEJM 2001; 344: 5

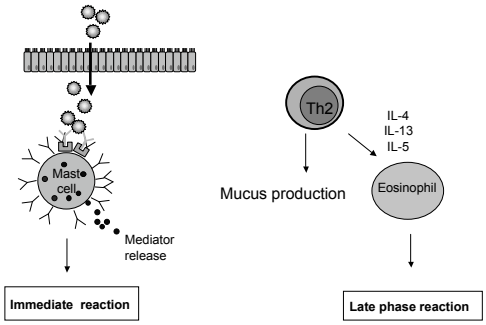
Airway changes – Inflammation and bronchoconstriction



Immunological mechanisms: Allergic sensitization



Immunological mechanisms: Reexposure



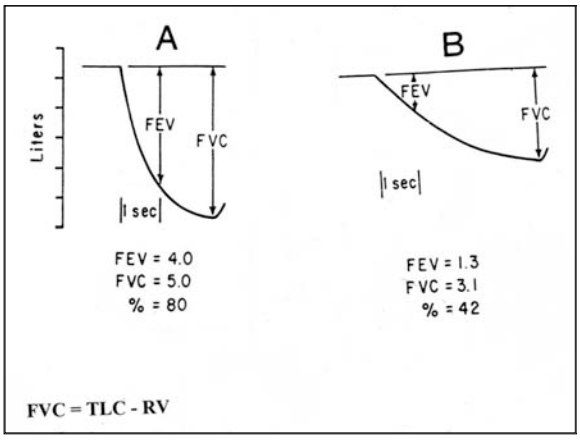
IgE-dependent release of inflammatory mediators

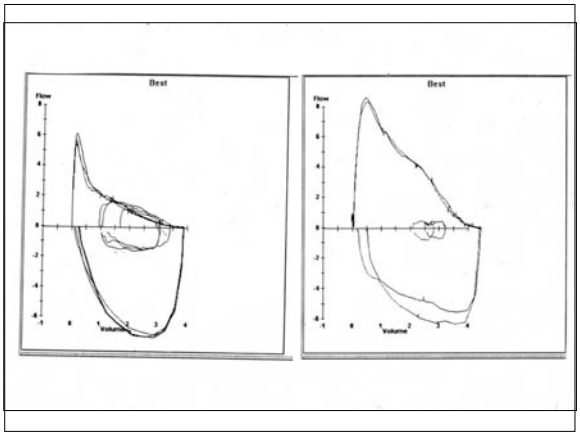
- Immediate: Granule contents
  - Histamine
  - TNF-a
  - Proteases
  - Heparin
- Over minutes: Lipid mediators
  - Prostaglandins
  - Leukotrienes
- Over hours: Cytokine production
  - IL-4
  - IL-13

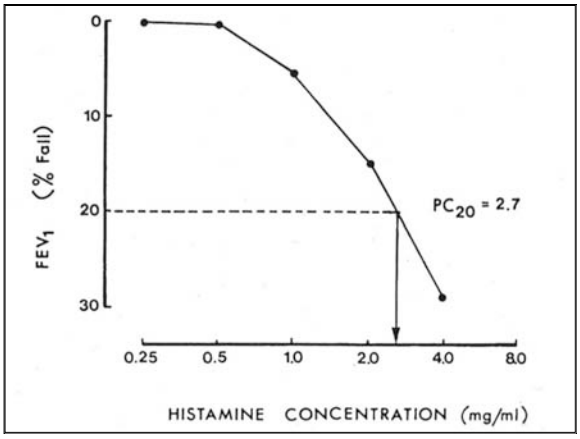
Diagnostic criteria for ssthma

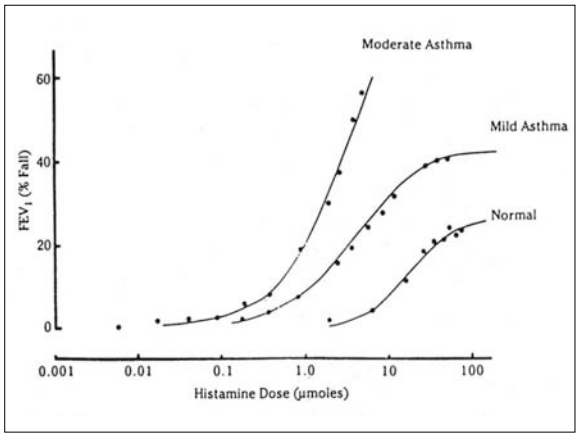
- CLINICAL DIAGNOSIS
- Cough, dyspnea, wheeze, chest tightness
- Waxing and waning symptoms
- Heightened airway reactivity –episodic airflow limitation in response to triggers.
- Airway hyperresponsiveness as measured by bronchoprovocation.

Methods for measuring airway caliber









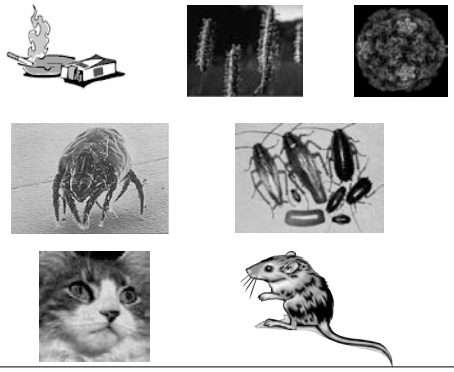
Physiologic features of asthma

- Reversible airflow limitation (obstructive defect)
  - >12% or 200ml change in FEV_1 in response to inhaled bronchodilator.
- Airway hyperresponsiveness
  - decrease in FEV_1 of 20% in response to bronchoprovocation testing (histamine, methacholine, cold air) in sensitive individuals. (Clinical trials, professional athletes)

Contributing factors to asthma exacerbation

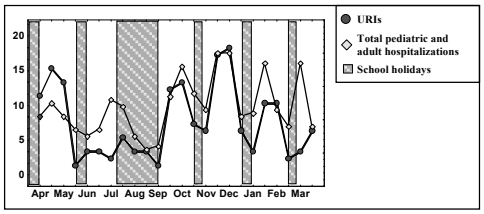
- Poorly controlled airway inflammation
- Cold air
- Exercise
- Upper respiratory tract infection
- Sinusitis, rhinitis
- GERD
- First or second hand tobacco smoke
- Environmental allergens – indoor and outdoor
- Air pollution

Asthma environmental triggers



VRIs and asthma hospitalizations

Hospital admissions correlate with virus isolation peaks and school terms.



Adapted 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 exacerbation

- Asthma trigger leads to bronchoconstriction and increase in airway inflammation– narrowing of airway lumen
- Increased resistance to airflow
- Reduction in FEV_1, peak flow
- Will reverse either spontaneously (eventually) or with use of medication (bronchodilators and anti-inflammatories)

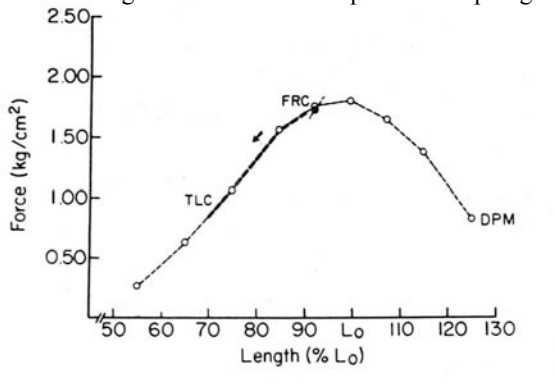
Gas exchange abnormalities in acute asthma exacerbation

- 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 pCO_2 "pseudo-normalizes" then becomes elevated.

Physical Exam

- PE of chest may be normal
- Wheezing or prolonged expiration
  - May not correlate with clinical severity
- Hyperinflation of lungs
- Use of accessory muscles

Length-tension relationship for the diaphragm



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 and oral corticosteroids
- Leukotriene modifiers
- Theophylline
- Cromolyn
- Long acting bronchodilators

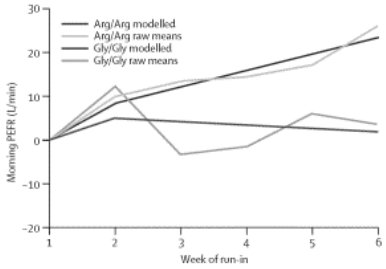
$ß_2$-agonists (Albuterol)

- Bind to $ß_2$ receptors on airway smooth muscle cells
  - cause relaxation of muscle and bronchial dilatation
- Most effective bronchodilators
  - short term relief of bronchoconstriction
- Rapid onset of activity
- Duration of action 3-6 hours.
- "rescue" therapy for symptom relief
- no advantage to regularly scheduled use
- no effect on chronic inflammation

Side effects of β_2 agonists

- Due to non-airway β_2 activity: skeletal muscle tremor
- Due to overlap β_1 activity: tachycardia, arrhythmia, hypokalemia
- Excessive use related to higher mortality and morbidity
  - marker for more severe disease?
- 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 β_2 adrenergic receptor



Israel; Lancet 2004

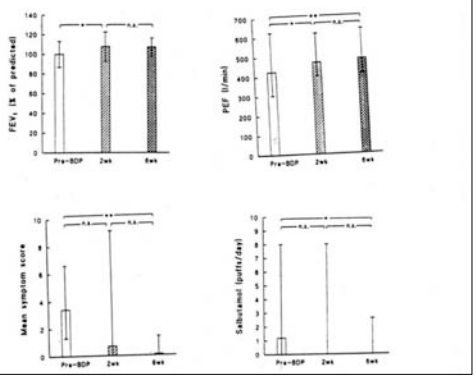
Glucocorticoids (Steroids)

- 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

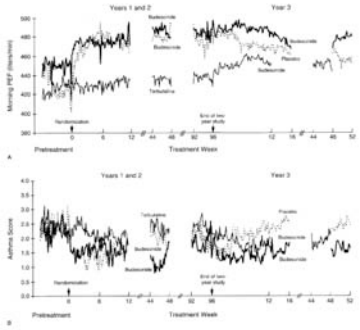
Inhaled glucocorticoids

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

SHORT TERM EFFICACY OF INHALED STEROIDS



Early initiation of inhaled corticosteroids preserves lung function

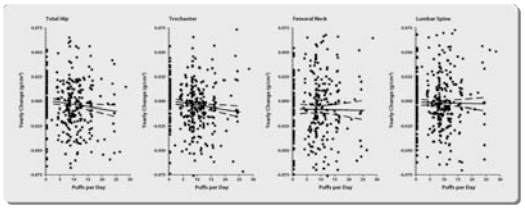


Haahtela, T. et al. N Engl J Med 1994;331:700-705

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.

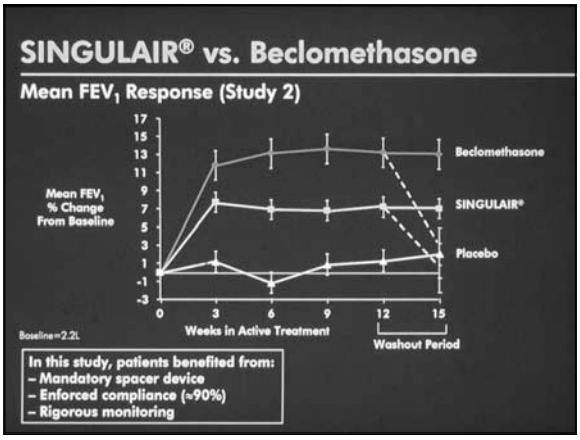
Bone density vs daily puffs of ICS



Israel, et al. *N Engl J Med* 2001;345:941-947.

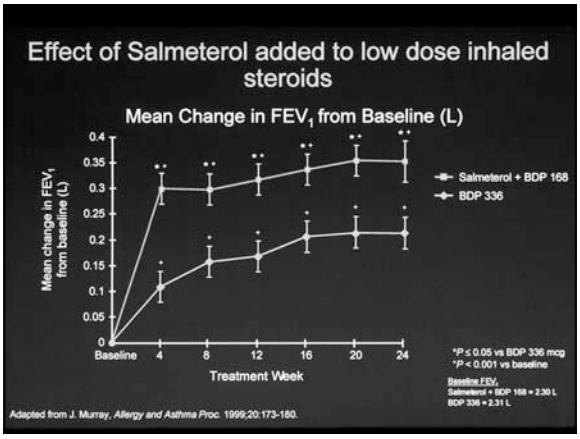
Leukotrienes

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



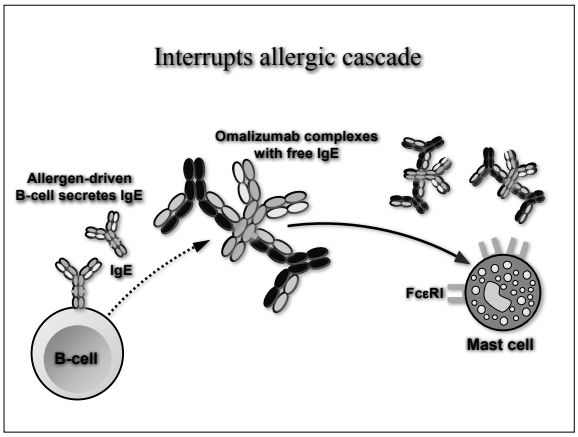
Long acting beta agonists

- Inhaled salmeterol (component of Advair®), 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
- Available as combination therapy in a single inhaler
- **New black box warning: Increased mortality and serious events in some patients taking long acting beta agonists, particularly African Americans**



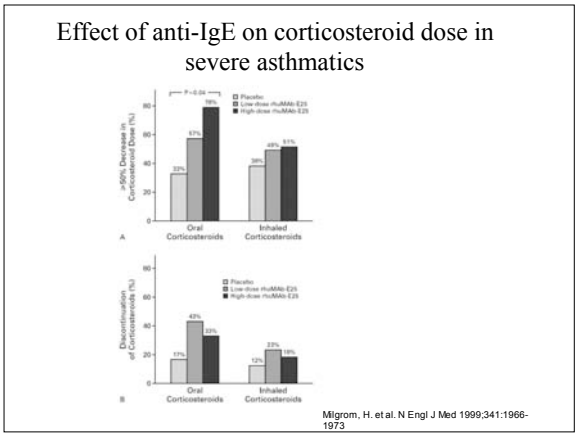
Biologics in treatment of asthma

- Targeted toward specific mediators
- 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 (IgE mediated) asthma
- Effective in reducing asthma exacerbation rate and reducing required corticosteroid dose
- Subcutaneous injections 1-2x/month



Asthma treatment

- NIH Guidelines, updated in 2007
- Assessment of asthma severity in initiating therapy
- Assessment of asthma impairment and asthma risk in adjusting therapy.

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
- Frequency of exacerbations and side effects from medications (assess risk which is a component of severity)

Assessment of asthma risk

- Frequency of exacerbations
- Side effects from medications
- Decline in lung function

NAEPP (2007) Guidelines for Asthma Severity classification

- Mild intermittent: symptoms < 2x/week, nocturnal symptoms < 2x/month, normal FEV_1
- Mild persistent: symptoms 3-6x/week, 3-4 awakenings/month, normal FEV_1
- Moderate persistent: daily symptoms, >5 nocturnal awakenings/month, FEV_1 60-80%
- Severe persistent: continual symptoms, FEV_1 < 60%

NIH Guidelines

- Patients with asthma symptoms more than twice per week should be on daily anti-inflammatory therapy.
- Inhaled steroids (rather than leukotriene modifiers) are the preferred first line therapy.

Long term control

- Immediate acting bronchodilators for acute symptom relief
- Step up anti-inflammatory therapy based on need for bronchodilators and frequency of symptoms
- Add second agent in suboptimally controlled asthma (LABA or leukotriene modifiers)
- Leukotriene modifiers and long acting β-agonist as steroid sparing agents.
- Frequent follow up to reassess symptoms and need to tailor therapy.

Treatment of acute asthma exacerbation

- High dose β_2 agonist (inhaled, SQ, IV)
- Nebulized anticholinergics
- Epinephrine
- Corticosteroids
- Oxygen
- Mechanical ventilation

Asthma that 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
- Use of biomarkers to assist with management (exhaled NO, PC20, sputum eosinophils)
- Identification of genes responsible for disease
- Better side effect profiles of drugs
- Biologics (monoclonal blocking antibodies)
- Th2/Th1 balance - vaccines
- Reduce racial disparities in asthma morbidity and mortality