Emily DiMango, MD
Asthma

Director

John Edsall/John Wood Asthma Center

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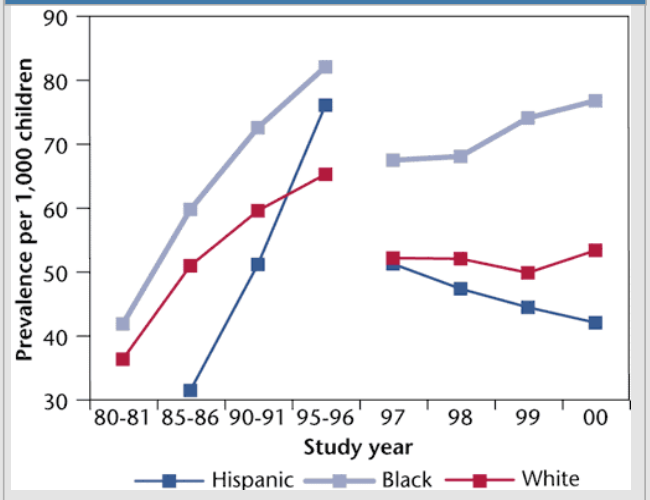
Figure 1
Asthma Prevalence, 1980-2000

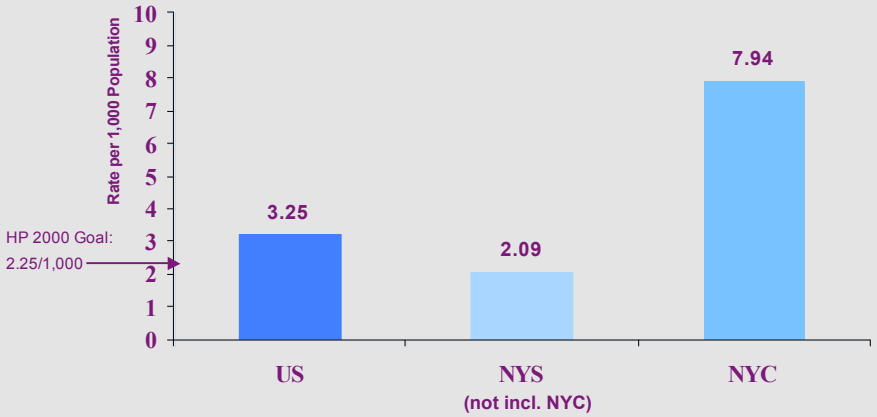


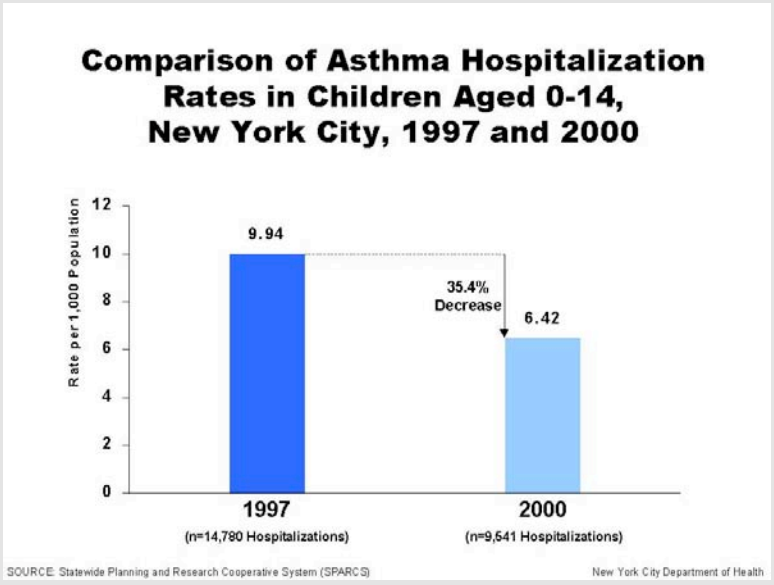
* Gap between 1995-1996 and 1997 indicates a break in trend due to the redesign of the 1997 NHIS.
Source: Data extracted from Akinbami and Schoendorf. *Pediatrics.* 2002.

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 U.S., NYS and NYC, 1999

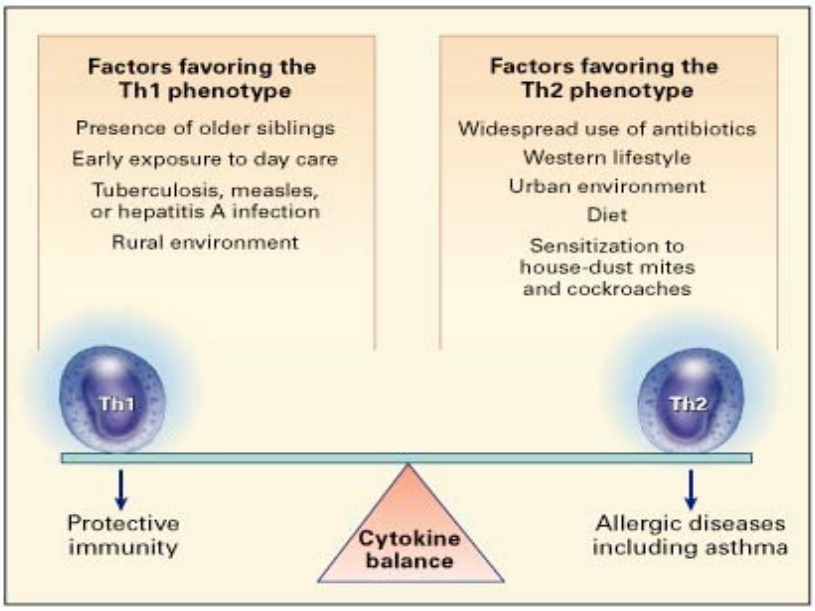




Risk factors for development of asthma

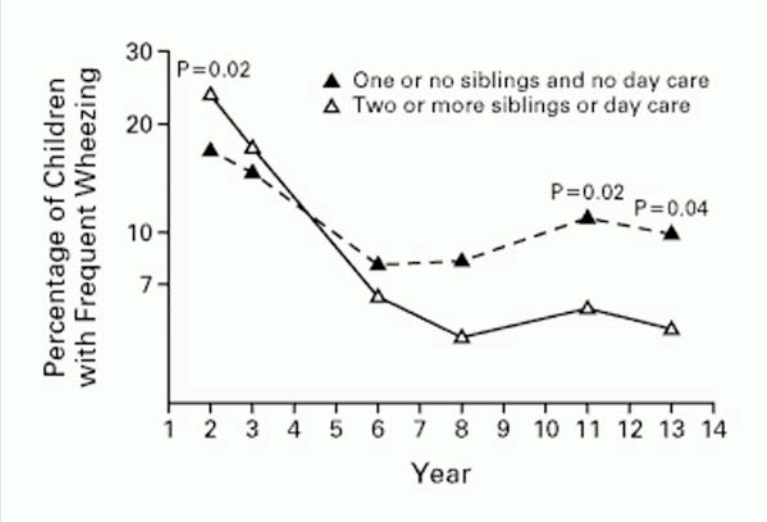
- Family history (genetics)
- Sensitization to common allergens
- Maternal smoking
- Obesity
- Western lifestyle

- ?? Diet, pollution



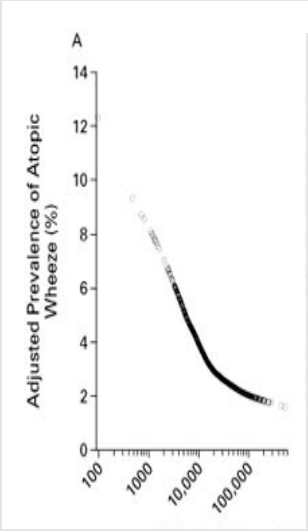
Busse, W., NEJM 2001; 344:5

Day care attendance in the first six months of life and/or presence of two or more older sibl associated with a reduced risk for developing asthma.



Ball T et al. N Engl J Med 2000;343:538-543

Effect of Endotoxin exposure on wheeze

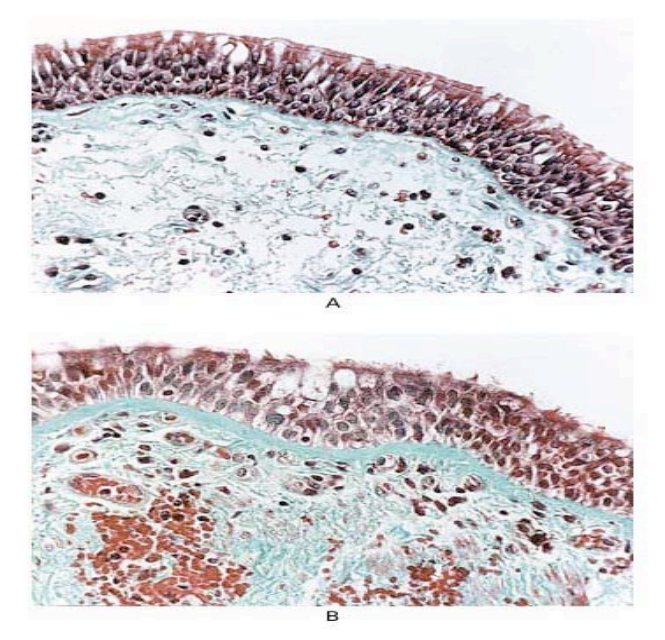


Endotoxin in mattress

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

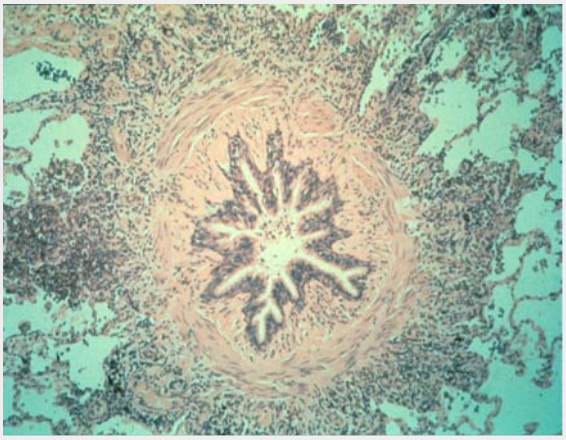
Asthma Definition

- 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

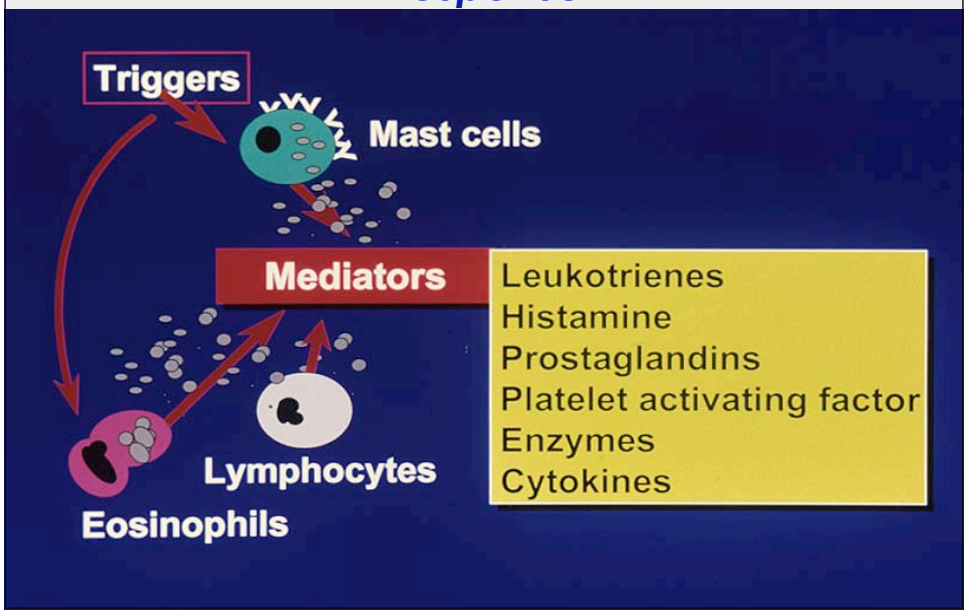


Busse, W, NEJM 2001; 344: 5

Airway Changes – Inflammation and bronchoconstriction

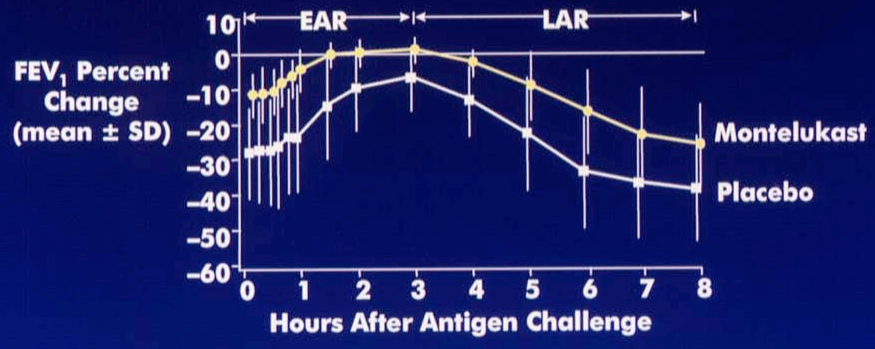


Airway inflammation - Early and late Response



Early and Late Asthmatic Response Following Antigen Challenge[24]

12-patient, 2-period crossover study



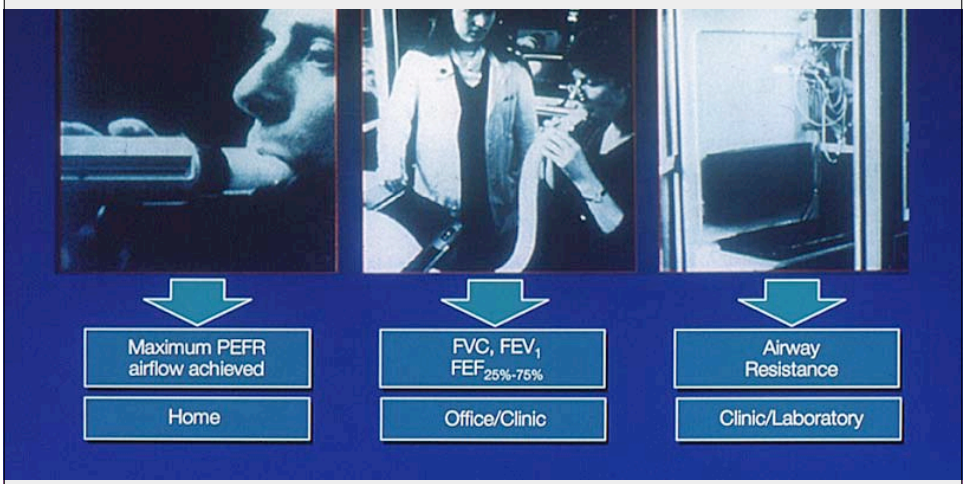
EAR = early asthmatic response; LAR = late asthmatic response

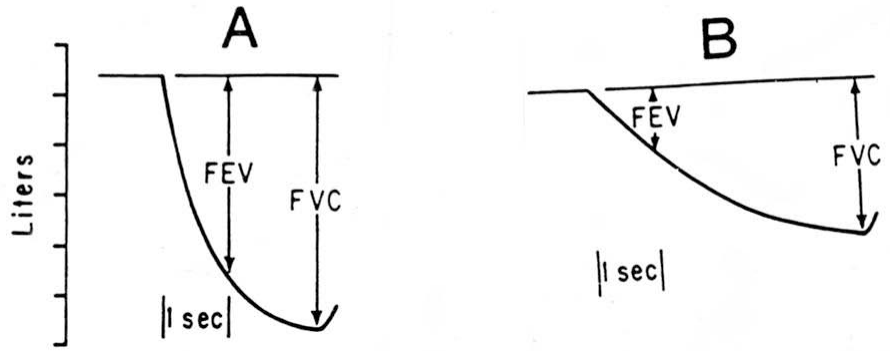
[24]Data on file at Merck & Co., Inc.: DA-SNG14.

Diagnostic Criteria For Asthma

- 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

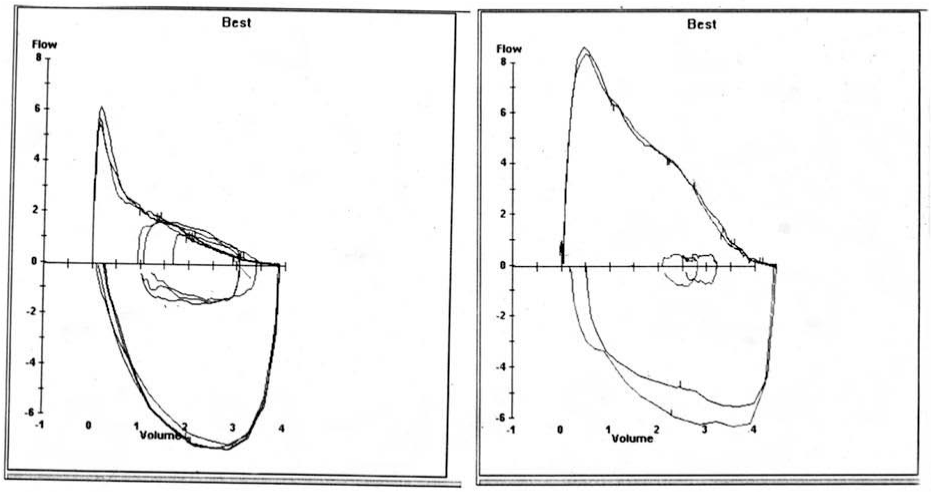


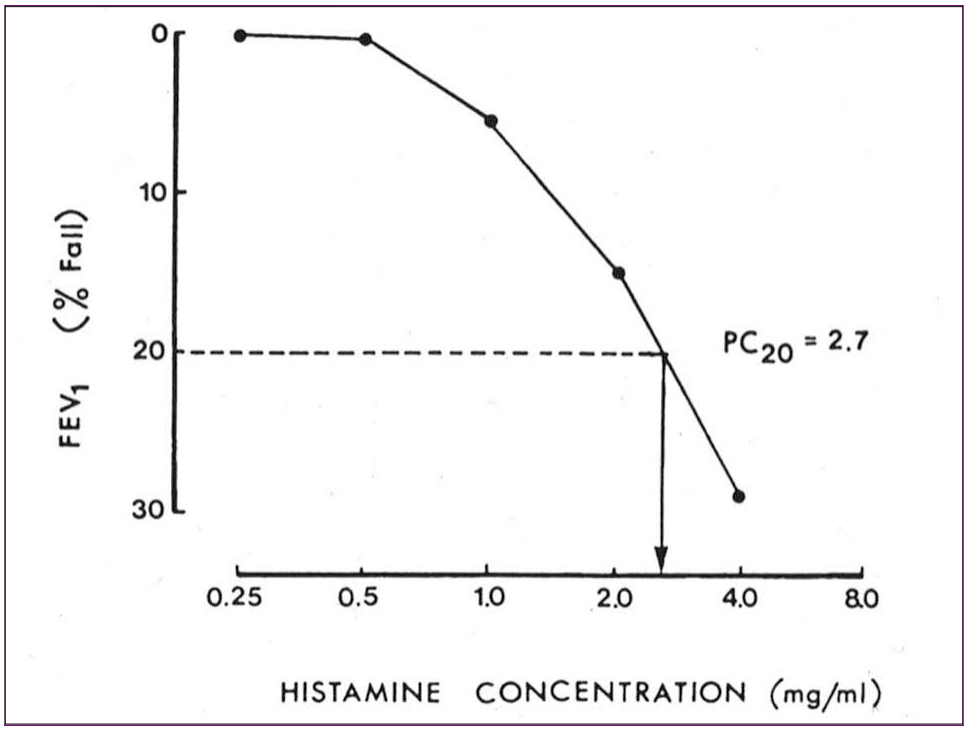


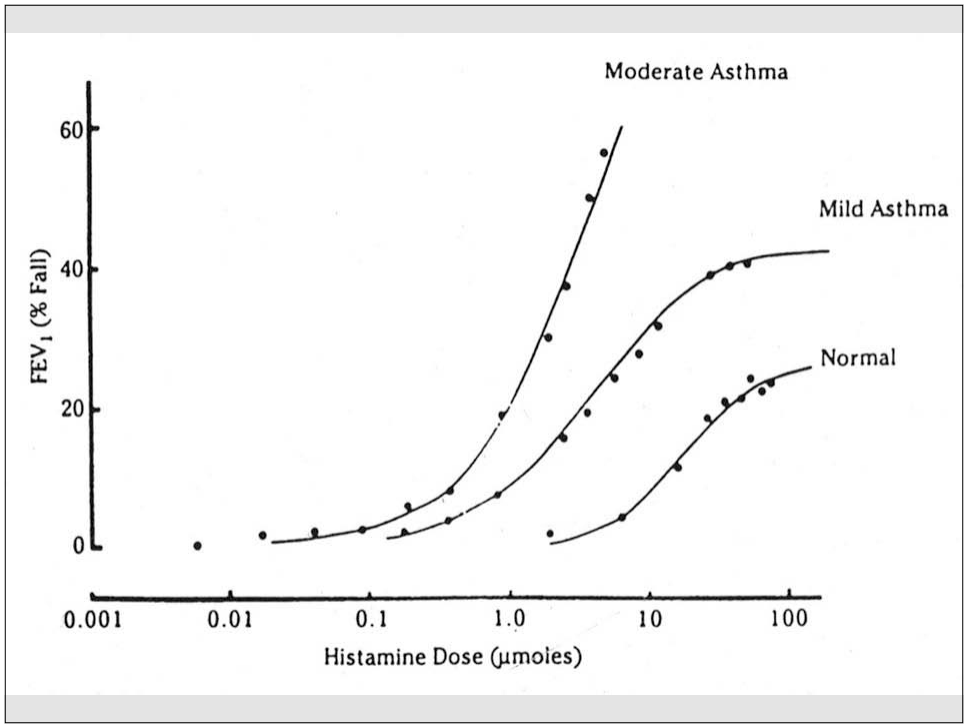
FEV = 4.0
FVC = 5.0
% = 80

FEV = 1.3
FVC = 3.1
% = 42

FVC = TLC - RV




0
10
20
30
FEV1 (% Fall)
PC20 = 2.7
0.25
0.5
1.0
2.0
4.0
8.0
HISTAMINE CONCENTRATION (mg/ml)


Moderate Asthma
Mild Asthma
Normal
60
40
20
0
FEV1 (% Fall)
0.001
0.01
0.1
1.0
10
100
Histamine Dose (μmoles)

Physiologic features of asthma

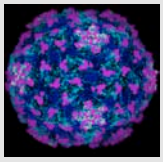
- Reversible airflow limitation (obstructive defect) with a significant (>12% or 200ml) change in FEV1 in response to inhaled bronchodilator.
- Airway hyperresponsiveness –decrease in FEV1 of 20% in response to bronchoprovocation testing (histamine, methacholine, cold air) in sensitive individuals. (Clinical 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

Asthma Environmental Triggers

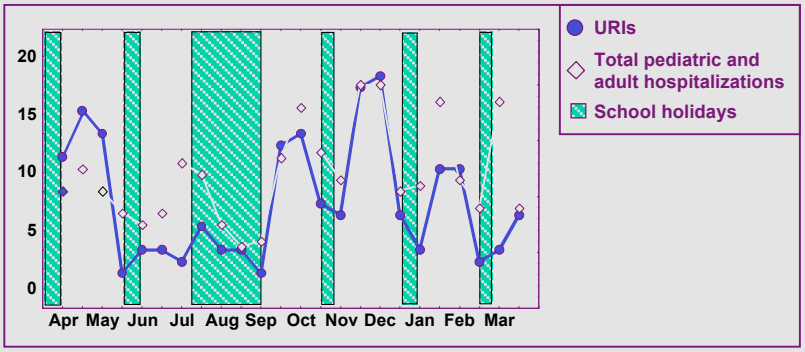






VRIs and asthma hospitalizations

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 FEV1, peak flow
- Will reverse either spontaneously (eventually) or with use of medication (bronchodilators and anti-inflammatories)

Gas exchange abnormalities in acute asthma exacerbation

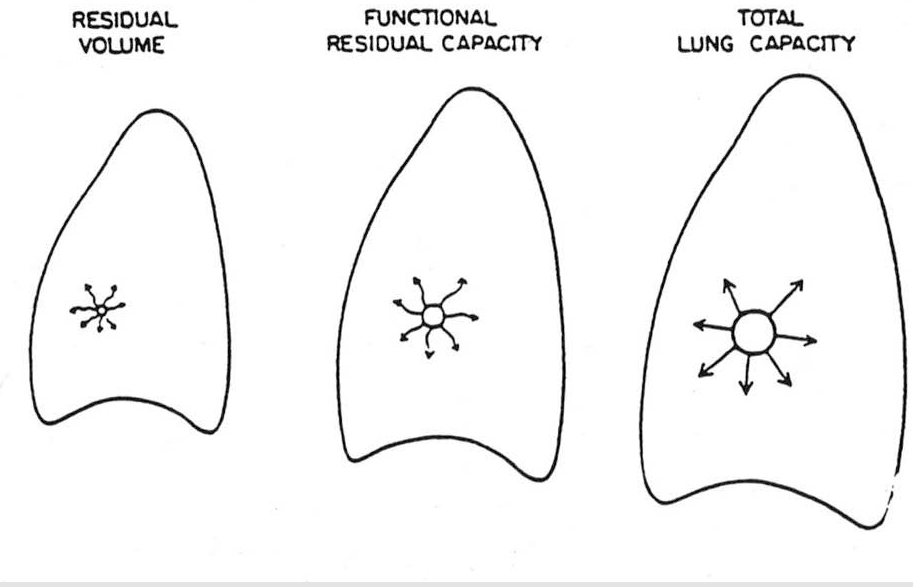
- Low V/Q leads to hypoxemia
- Increased ventilatory drive leads to reduction in pCO2.
- As severity of airflow obstruction increases, respiratory muscle fatigue develops and pCO_2 "pseudo-normalizes" then becomes elevated.

Physical Examination

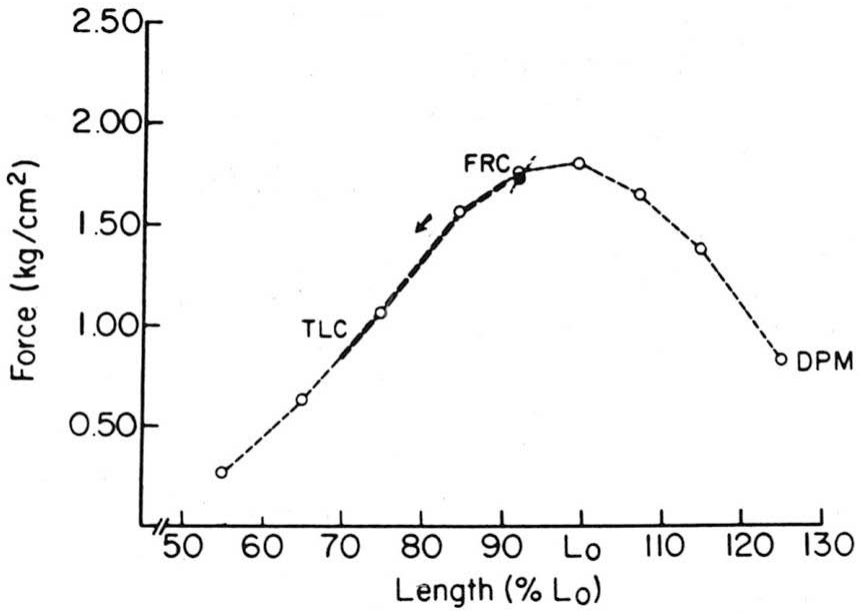
Physical examination of the chest may be normal.

- **Wheezing or prolonged force expiration**
  - **may not correlate with obstruction**
- **Hyperinflation of the lungs**
- **Use of accessory muscles**

Relationship between lung volume and airway caliber



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

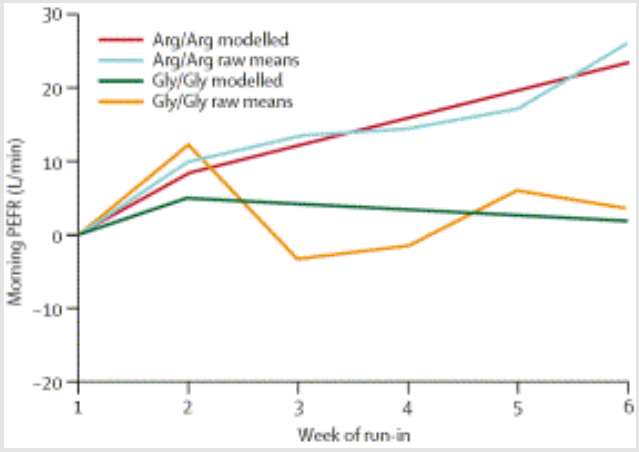
$ß_2$-agonists (Albuterol)

- Bind to $ß_2$ receptors on airway smooth muscle cells, cause relaxation of muscle and bronchial dilatation
- Most effective bronchodilators available, 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 b_2 agonists

- Due to non-airway b_2 activity: skeletal muscle tremor
- Due to overlap b_1 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.

Effect of polymorphisms at the amino acid residue 16 locus of the B_2 adrenergic receptor



Israel; Lancet 2004

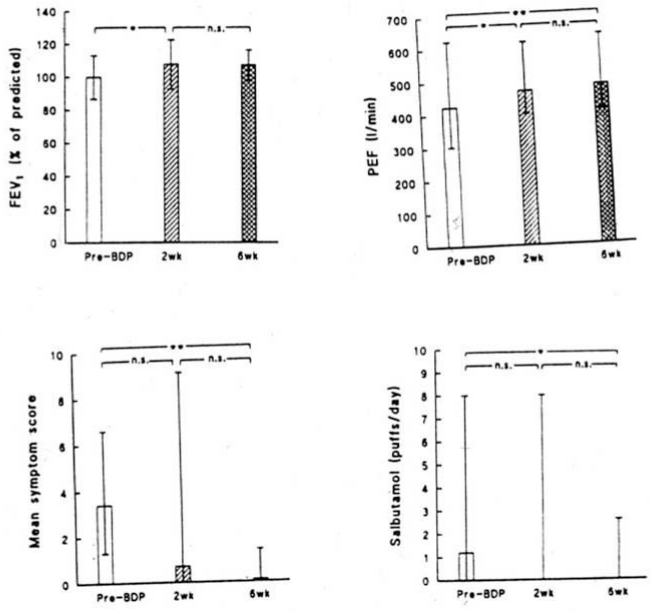
Glucocorticoids (Steroids)

- 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

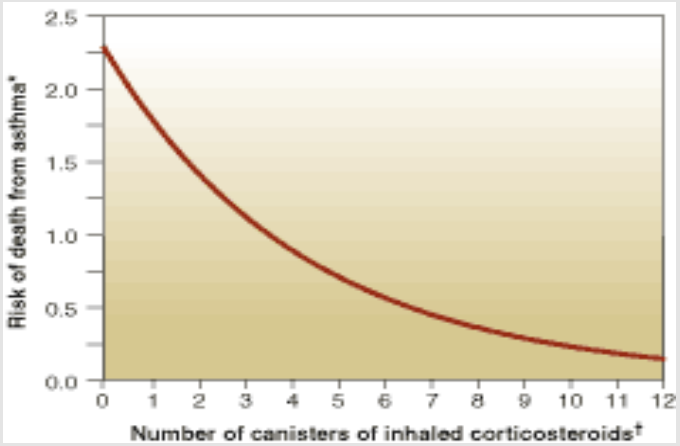
Inhaled glucocorticoids

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

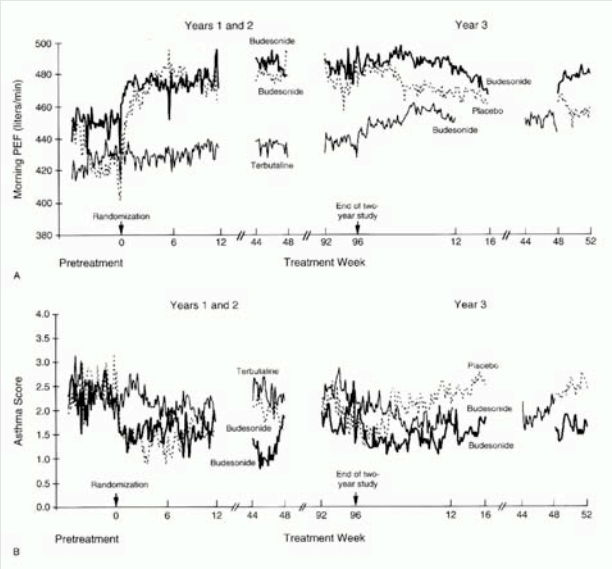
SHORT TERM EFFICACY OF INHALED STEROIDS



Risk of death from asthma is inversely related to number of cannisters of inhaled steroids

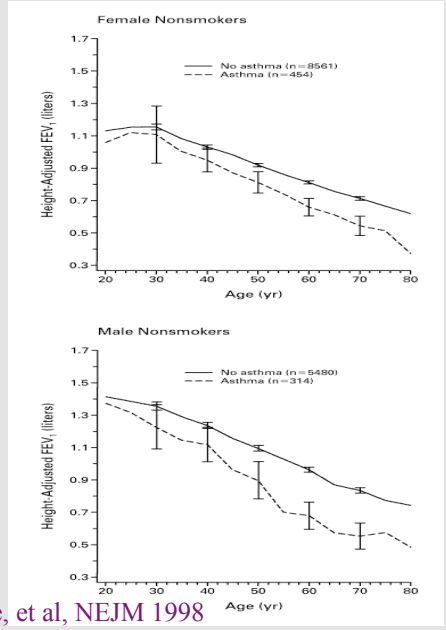


Early initiation of inhaled corticosteroids preserves lung function



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

Accelerated decline in lung function among asthmatics

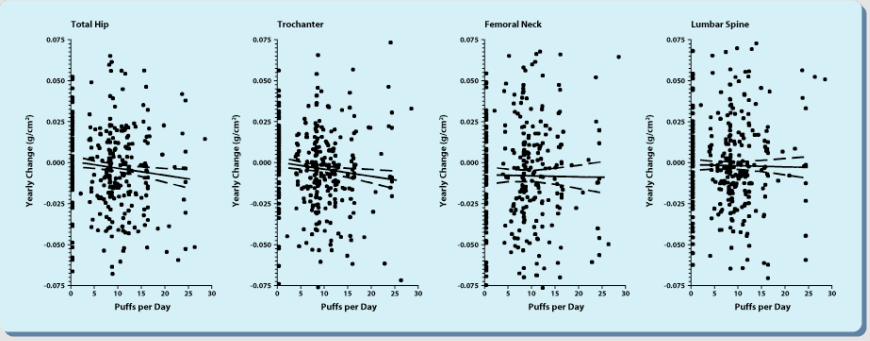


Lange, et al, NEJM 1998

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.

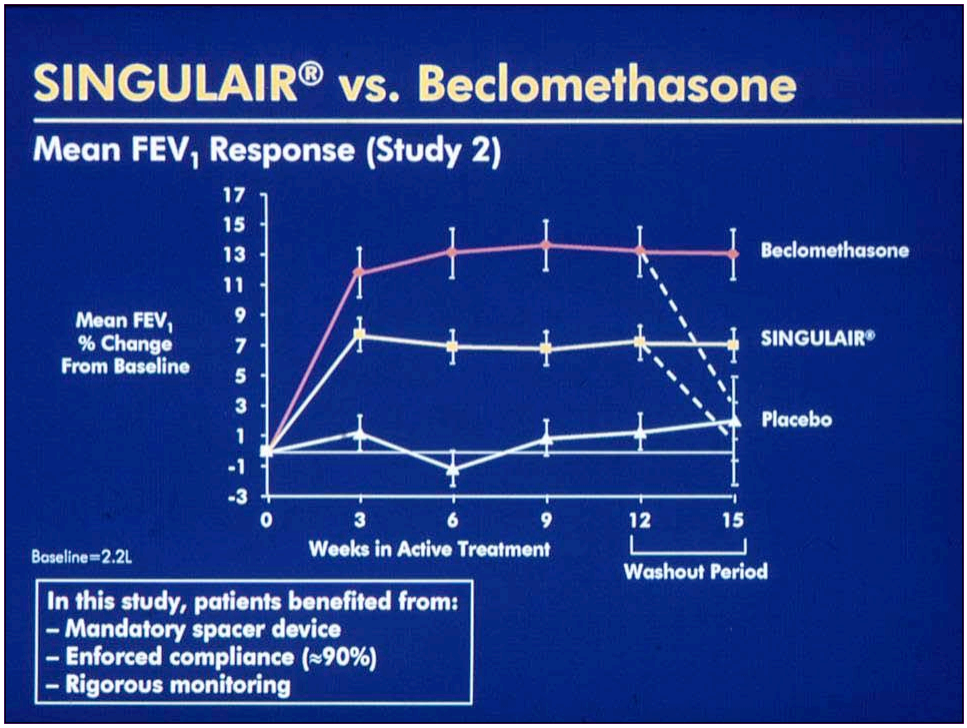
Bone Density vs Daily Puffs of ICS



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

Leukotrienes in Asthma

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

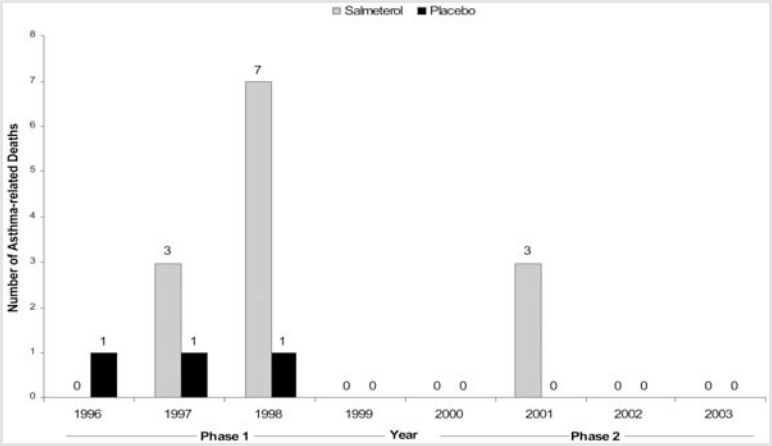


Long acting beta agonists

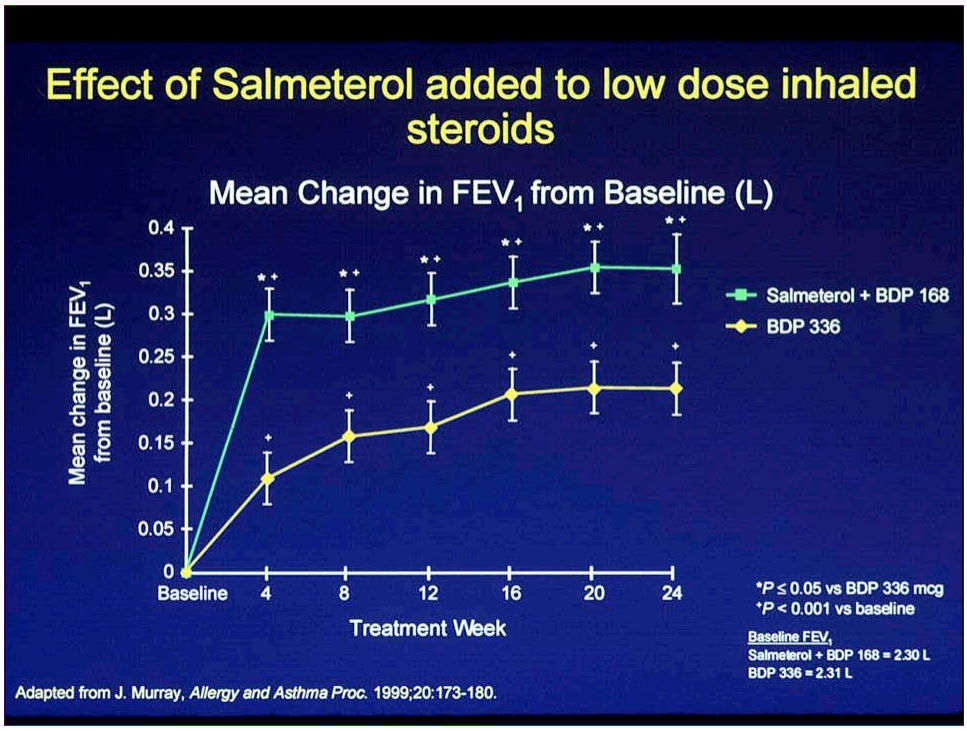
- Inhaled salmeterol (component of Advair®)and formoterol
- Duration of action 12 hours, bid drug
- Delayed onset of action (30 minutes)
- Efficacious in moderate to severe asthma
- Allow reduction of inhaled steroid dose
- **Not monotherapy**; ie use only as add on therapy to anti inflammatory agents – avoid masking of inflammation
- 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**

Occurrence of asthma-related deaths by phase and study year



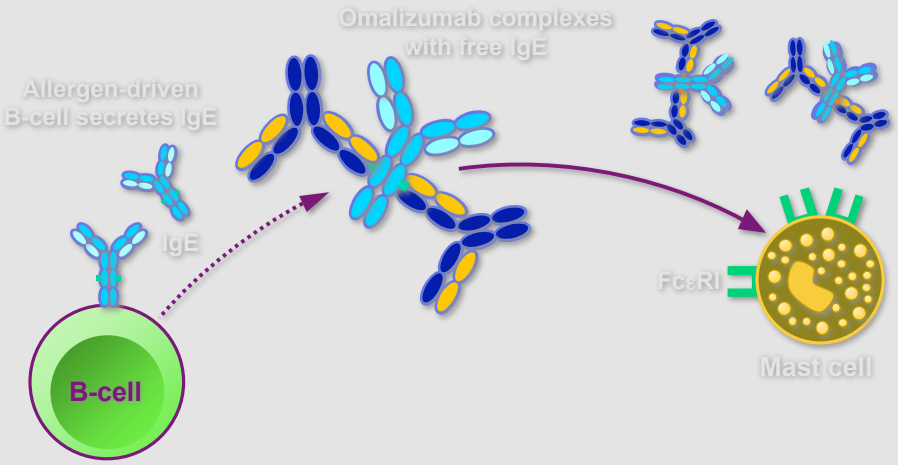
Nelson, H. S. et al. Chest 2006;129:15-26



Biologics in treatment of asthma

- Targeted toward specific mediators
- Monoclonal Ab-IgE is first compound commercially available.
- Expensive

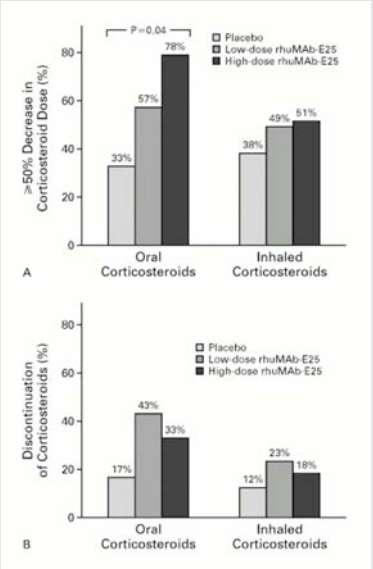
Interrupts allergic cascade



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

Effect of anti-IgE on corticosteroid dose in severe asthmatics



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

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 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%

NIH Guidelines

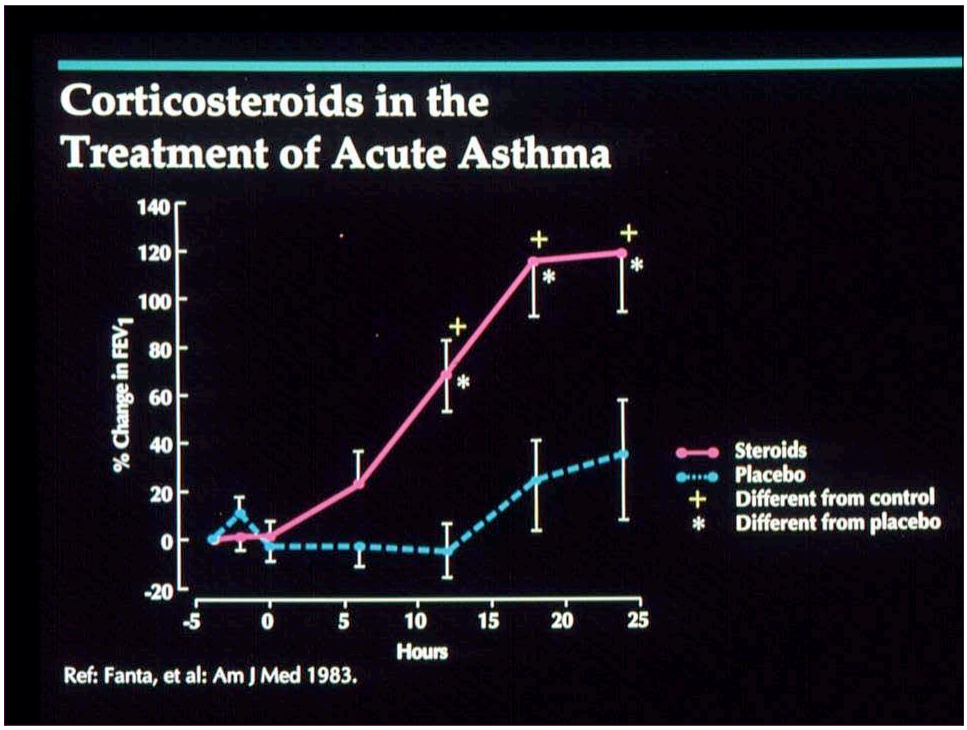
- **Patients with asthma symptoms more than twice per week should be on daily anti-inflammatory therapy.**
- Inhaled steroids (rather than leukotriene modifiers) are the preferred first line therapy.

Long term control of asthma

- Use 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)
- Can use leukotriene modifiers and long acting b-agonist as steroid sparing agents.
- Frequent follow up to reassess symptoms and need to tailor therapy.

Treatment of acute asthma exacerbation

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



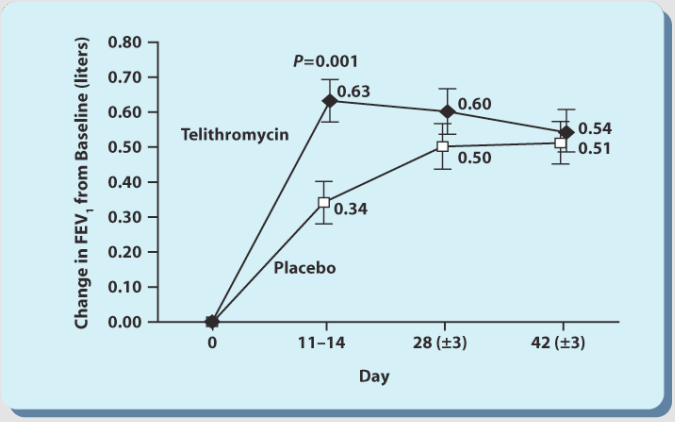
Asthma which is difficult to control

- 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

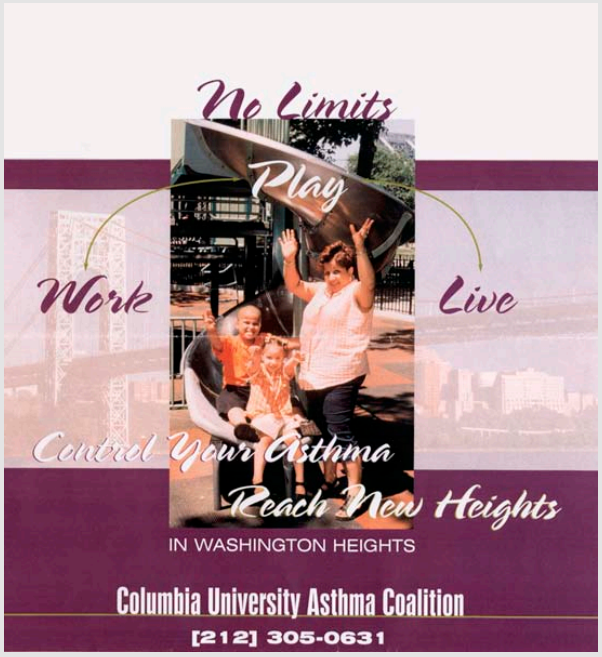
Future Goals

- 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
- Asthma as an infectious disease?

Mean Changes in FEV_1 From Baseline



Johnston, et al. *N Engl J Med* 2006; 345:1589-1600.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Work
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Reach New Heights
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