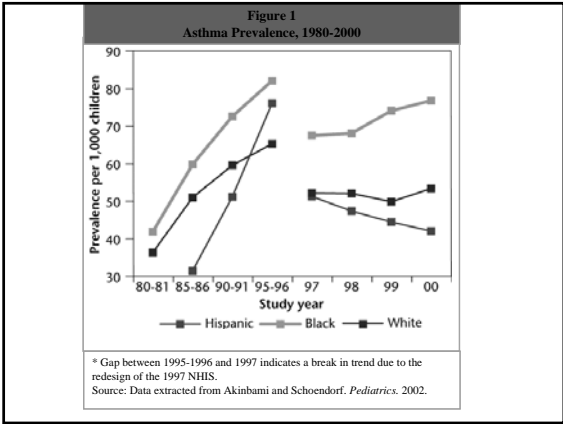
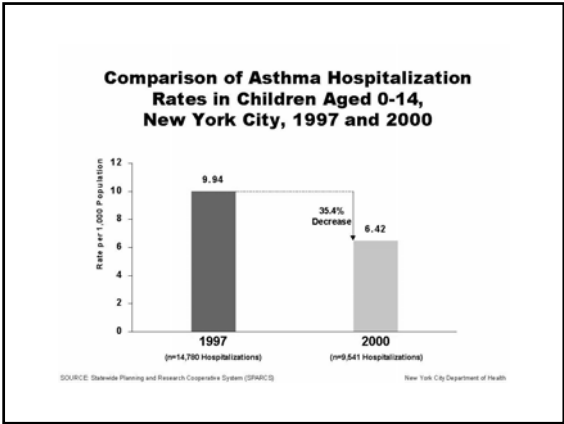
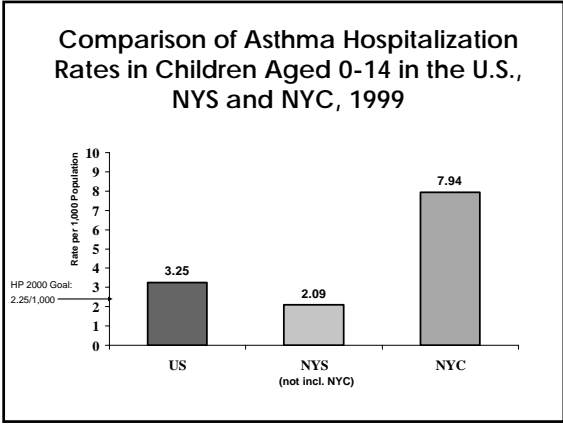


**Emily DiMango, MD**  
**Asthma II**  
 Director  
 John Edsall/John Wood Asthma  
 Center  
 Columbia University Medical Center



**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



**Risk factors for development of asthma**

- Family history
- Sensitization to common allergens
- Maternal smoking
- Obesity
- Western lifestyle
- ?? Diet, pollution

## Protective associations

- Cat and dog exposure in early life (protects against all allergen sensitization)
- Exposure to farm animals in early life (endotoxin)
- Day care in first 6 months of life
- Multiple siblings

Owby, et al. JAMA 2002  
Braun-Fahrlander, et al. NEJM 2002

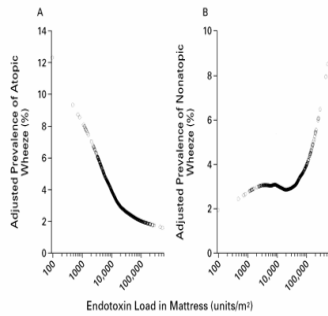
Percentage of Children with Asthma According to the Number of Older Siblings and the Age at Entry into Day Care

**TABLE 1. PERCENTAGE OF CHILDREN WITH ASTHMA ACCORDING TO THE NUMBER OF OLDER SIBLINGS AND THE AGE AT ENTRY INTO DAY CARE.** *Bali M NEJM 2000*

VARIABLE	NO. OF CHILDREN*	ASTHMA %	RELATIVE RISK (95% CI)†	P VALUE
No. of older siblings‡				
0	405	21	1.0	
1	385	19	0.9 (0.7-1.0)	0.04
2	176	14	0.7 (0.5-1.0)	0.04
≥3	69	13	0.6 (0.4-1.0)	0.04
Age at entry into day care				
>12 mo	899	19	1.0	
7-12 mo	28	18	0.9 (0.4-2.1)	0.88
Birth to 6 mo	69	9	0.4 (0.2-1.0)	0.03

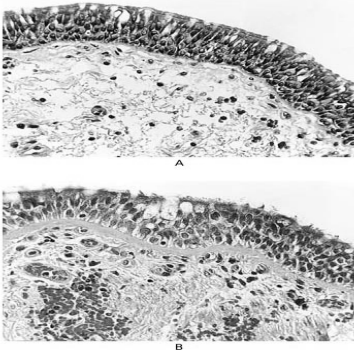
## Effect of Endotoxin exposure on wheeze

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



## Asthma Definition

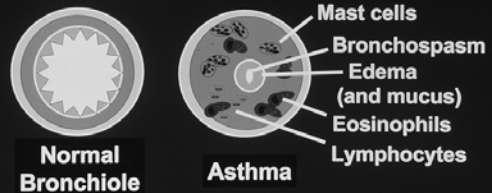
- Chronic inflammatory disorder of the airways
- Usually associated with atopy (extrinsic, intrinsic)
- Obstruction to airflow which is reversible (either spontaneously or with use of medications)
- Airway hyperresponsiveness and narrowing in response to a variety of stimuli



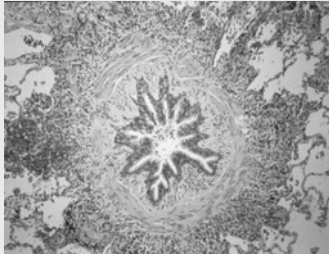
Busse, W, NEJM 2001; 344: 5

## Asthma: A Lung Disease with Airway

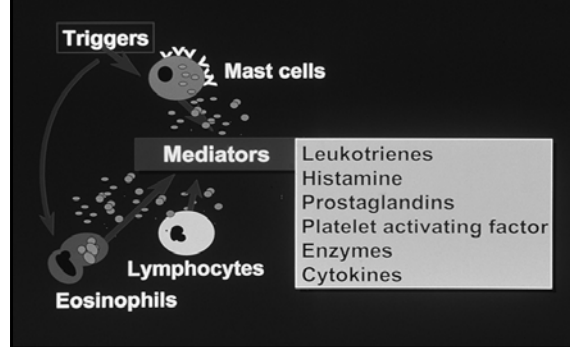
- Obstruction (at least partially reversible)
- Hyperreactivity
- Inflammation



### Airway Inflammatory Changes

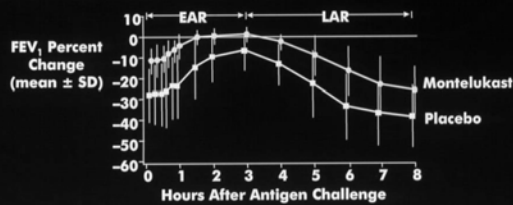


### Airway inflammation - Early and late Response



### Early and Late Asthmatic Response Following Antigen Challenge<sup>24</sup>

12-patient, 2-period crossover study



EAR = early asthmatic response; LAR = late asthmatic response

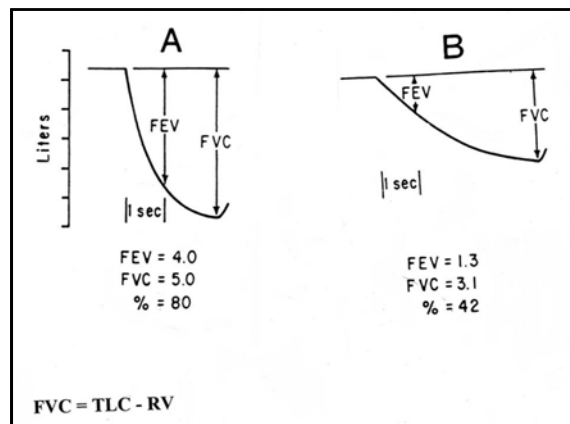
<sup>24</sup>Data on file at Merck & Co., Inc.: DA-5NG14.

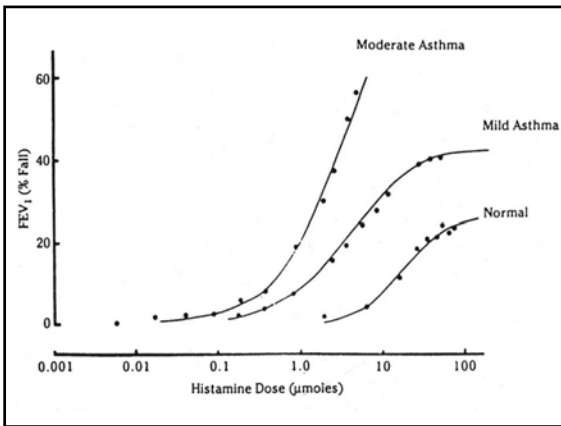
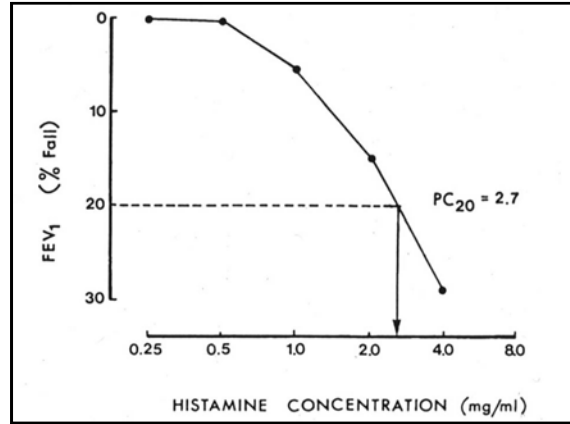
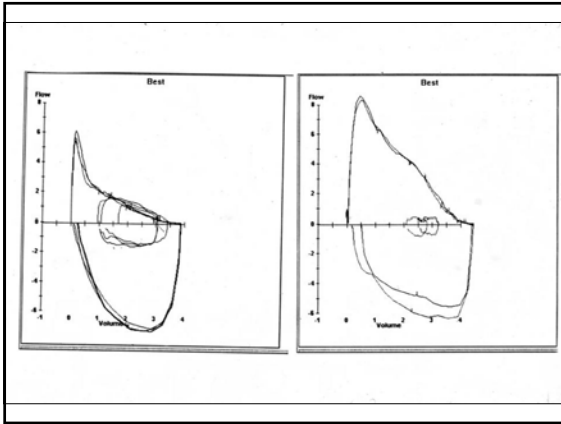
### Diagnostic Criteria For Asthma

- Cough, dyspnea, wheeze, chest tightness
- Waxing and waning symptoms
- Heightened airway reactivity – exacerbations upon exposure to stimuli
- Episodic airflow limitation in response to antigenic triggers.

### Physiologic features of asthma

- Reversible airflow limitation (obstructive defect) with a significant (>12%) change in FEV1 in response to inhaled bronchodilator.
- response to bronchoprovocation testing - challenge with agent (histamine, cold air) which provokes bronchial narrowing (decrease of 20% in FEV1) in sensitive individuals. (Clinical trials, professional athletes)





### Methods For Measuring Airway Caliber

Three photographs illustrating different methods for measuring airway caliber. Below each photo is a box indicating the measurement and the typical setting:

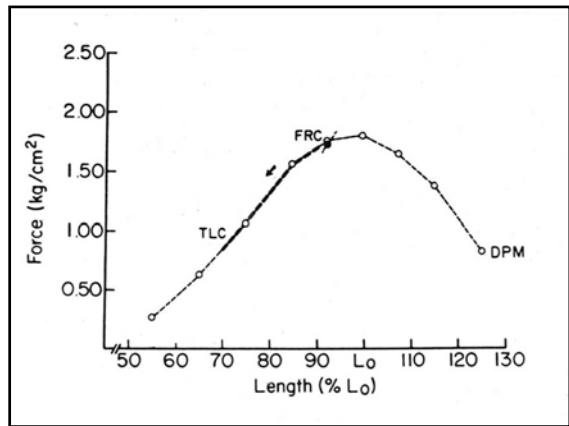
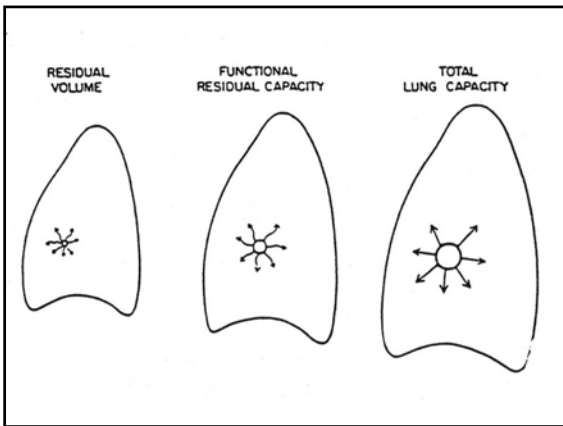
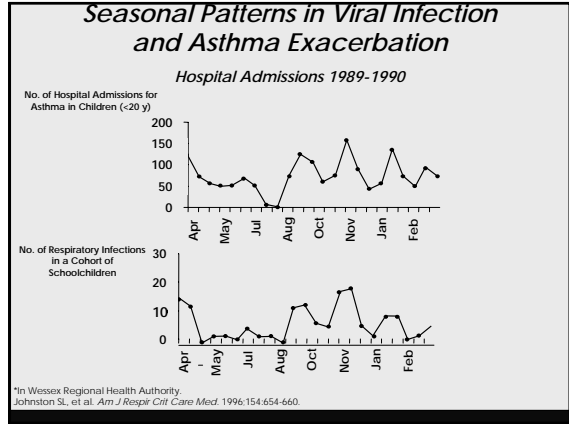
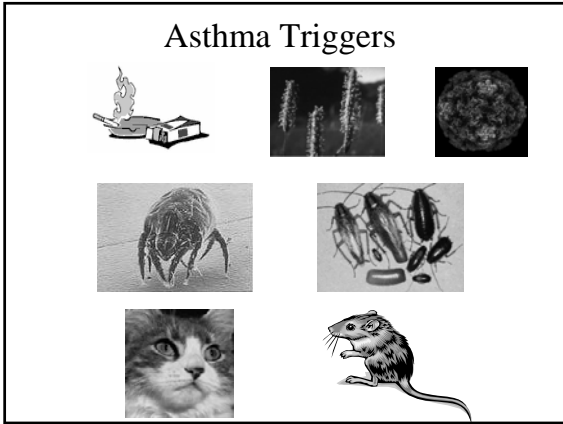
- Maximum PEFR airflow achieved (Home)
- FVC, FEV<sub>1</sub>, FEF<sub>25%-75%</sub> (Office/Clinic)
- Airway Resistance (Clinic/Laboratory)

### Asthma exacerbation

- Asthma trigger leads to bronchoconstriction and increase in airway inflammation—narrowing of airway lumen
- Increased resistance to airflow
- Reduction in FEV<sub>1</sub>, 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

- Low V/Q leads to hypoxemia
- Increased ventilatory drive leads to reduction in pCO<sub>2</sub>.
- As severity of airflow obstruction increases, respiratory muscle fatigue develops and pCO<sub>2</sub> “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

## 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 corticosteroids
- Leukotriene modifiers
- Theophylline
- Cromolyn
- Long acting bronchodilators

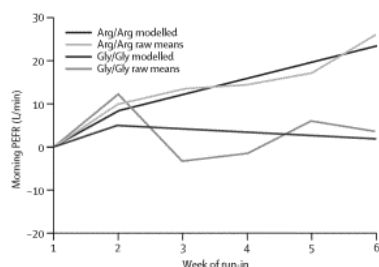
## $\beta_2$ -agonists (Albuterol)

- 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

## Side effects of $\beta_2$ agonists

- Due to non-airway  $\beta_2$  activity: skeletal muscle tremor
- Due to overlap  $\beta_1$  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  $\beta_2$  adrenergic receptor



## 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

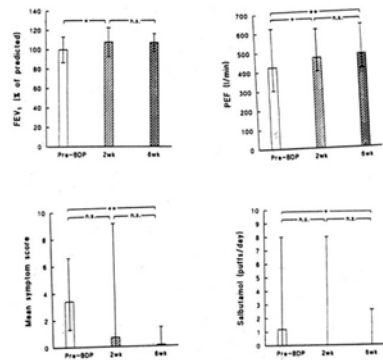
## Inhaled glucocorticoids

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

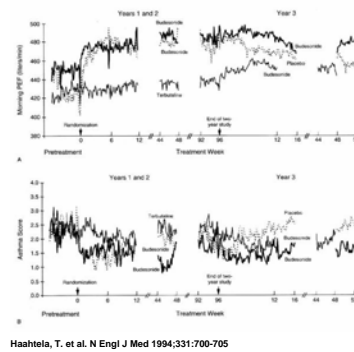
## Side effects of inhaled steroids

- Thrush and dysphonia are local effects
- Potential systemic effects: growth retardation, adrenal suppression, osteoporosis, cataracts, acne, skin fragility with high doses.

### SHORT TERM EFFICACY OF INHALED STEROIDS

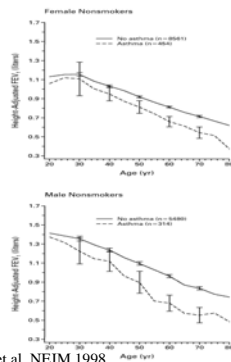


### Early initiation of inhaled corticosteroids preserves lung function



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

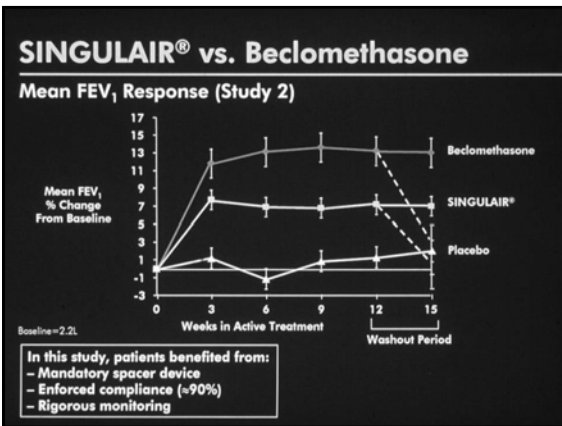
### Accelerated decline in lung function among asthmatics



Lange, et al, NEJM 1998

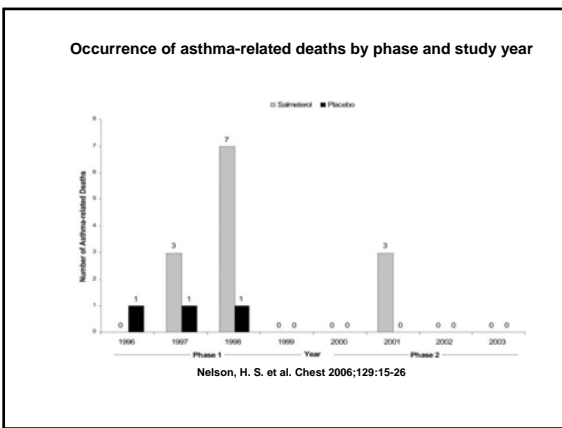
## Leukotrienes in Asthma

- 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
- **New black box warning: Increased mortality and serious events in some patients taking long acting beta agonists, particularly African Americans**



### 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  $\beta_2$  agonists
- Additive when used in combination with  $\beta_2$  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

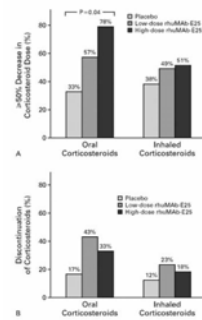
## Biologics in treatment of asthma

- Targeted toward specific mediators
- Anti-IL5 tested, not efficacious
- 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 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

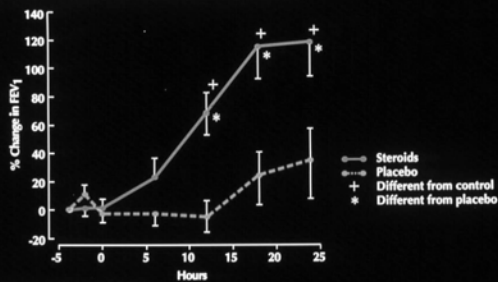


Milgrom, H. et al. N Engl J Med 1999;341:1966-1973

## Treatment of acute asthma exacerbation

- High dose  $\beta_2$  agonist (inhaled, SQ, IV)
- Nebulized anticholinergics
- epinephrine
- Corticosteroids
- Oxygen
- Mechanical ventilation

## Corticosteroids in the Treatment of Acute Asthma



Ref: Fanta, et al: Am J Med 1983.

## 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

### *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 racial disparities in asthma morbidity and mortality

