Asthma

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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

- 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

![Bar chart showing hospitalization rates per 1,000 population for US, NYS, and NYC. US: 3.25, NYS: 2.09, NYC: 7.94. HP 2000 Goal: 2.25/1,000.](chart.png)
Risk factors

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

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

Reprinted Ball TM et al. N Engl J Med. 2000;343:538. Copyright ©2000 Massachusetts Medical Society. All rights reserved.
Effect of endotoxin exposure on wheeze

Endotoxin in mattress


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
Airway changes –
Inflammation and bronchoconstriction
Immunological mechanisms:
Allergic sensitization

- MHC Class II protein and epitope
- Antigen-specific IgE
- IL-4, IL-13, IL-5
- Eosinophil
- Mucus production

Immediate reaction
Late phase reaction
IgE-dependent release of inflammatory mediators

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

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

A

\[
\text{FEV} = 4.0 \\
\text{FVC} = 5.0 \\
\% = 80
\]

B

\[
\text{FEV} = 1.3 \\
\text{FVC} = 3.1 \\
\% = 42
\]

\[\text{FVC} = \text{TLC} - \text{RV}\]
Physiologic features of asthma

• Reversible airflow limitation (obstructive defect)
  – >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
- Air pollution

Asthma environmental triggers
VRIs and asthma hospitalizations

Hospital admissions correlate with virus isolation peaks and school terms.

![Graph showing VRIs and asthma hospitalizations]


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 pCO2 “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
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

**β₂-agonists (Albuterol)**
- Bind to β₂ 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 $\beta_2$ 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
  - 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 $\beta_2$ adrenergic receptor

[Graph showing the effect of different polymorphisms on morning PEF (L/min) over weeks]

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
Early initiation of inhaled corticosteroids preserves lung function

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

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

![Effect of Salmeterol added to low dose inhaled steroids](image-url)
Biologics in treatment of asthma

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

Interrupts allergic cascade

- Allergen-driven B-cell secretes IgE
- Omalizumab complexes with free IgE
- IgE binds to FcεRI on Mast cell
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

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 $\beta_2$ 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