Asthma

Rachel L. Miller M.D., FAAAAI
Associate Professor of Medicine (in Pediatrics) and
Environmental Health Sciences
Program Director, Allergy and Immunology
Columbia University College of Physicians and Surgeons
Asthma Definition

Asthma is a chronic inflammatory disorder of the airways characterized by airway hyperresponsiveness, airflow obstruction, and clinical symptoms.
Bronchial Wall in Asthma

A. Normal

B. Asthma

- Mucus in airway
- Mucosal edema
- Increased mucous glands
- Contracted hypertrophied muscle
Flow volume loop: Airflow obstruction

![Flow volume loop diagram](image)

- Normal
- Obstructive

Flow rate (l/sec) vs. Exhaled vital capacity (%)

- $V_{\text{max}50\%}$
- $V_{\text{max}75\%}$
Reversible Airflow Obstruction

- Improvement in FEV$_1$ and/or FVC after an inhaled bronchodilator
- 12% relative increase AND 200 ml increase is “significant”
- Smaller improvements may still be important
Bronchial Hyperresponsiveness

- Patient breathes in nebulized methacholine or histamine
- Both drugs provoke bronchoconstriction that can then be quantified by spirometry
- People with pre-existing airway hyperreactivity, such as asthmatics, will react to lower doses of drug
- Decline in FEV1 of 20% from your baseline reading is considered a positive test.
Gas exchange in asthma

• Gas exchange is normal between attacks
• During attacks
  – V/Q mismatch causes hypoxemia
  – Typically mild
  – May be severe
Alveolar Ventilation in Asthma

• During an attack….
  – Alveolar hyperventilation nearly universal
    • Due to increased minute ventilation
• When severe…
  – Alveolar hypoventilation can occur
    • Due to respiratory muscle fatigue and increased dead space
    • Can be fatal!
Asthma symptoms

• Asthma is an episodic disease
• Between attacks
  – Symptoms vary depending on “asthma control”
  – Nocturnal symptoms are common
• During attacks
  – Wheeze
  – Cough
  – Chest tightness
Differential diagnosis of wheezing

- Upper airway obstruction
- Lower airway obstruction
  - Asthma
  - COPD
  - Cystic fibrosis & bronchiectasis
  - Large airway obstruction
    - Tumor, stenosis, foreign body aspiration, et al.
    - Bronchiolitis
    - Pulmonary edema
    - Carcinoid syndrome
Why learn about asthma?
Ever asthma diagnosis, US, 2005, adults*

*23 million adults lifetime asthma diagnosis

Age-adjusted based on 2000 census
Source: CDC/NCHS/National Health Interview Survey
Asthma deaths, 2003*

Per 100,000 Population
*3780 asthma deaths 2004, or 1.3/100,000, or > 10 people/day

Age-adjusted based on 2000 census
Source: CDC/NCHS/National Health Interview Survey
Asthma Causes and Triggers
Causes of Asthma

- Genetic and/or epigenetic predisposition;
  - FCE R1, CD14, IL-4, IFNγ, B2AR; ACSL3*
- Environment
  - Allergic sensitization, fewer sibs, excessive hygiene, prenatal antibiotic exposure, vaccination, farm
- Prenatal exposures
  - Parent of origin effect for IgE, asthma; maternal parity; maternal smoking
- Prenatal diet
  - Increased methyl donors; reduced zinc, vitamin E, vitamin D, zinc; Mediterranean diet

* Studied at Columbia

Pathogenesis of Asthma

Key: LRI, lower respiratory illnesses; RSV, respiratory syncytial virus; PIV, parainfluenza virus
Cytokine Balance

Factors favoring the Th1 phenotype
- Presence of older siblings
- Early exposure to day care
- Tuberculosis, measles, or hepatitis A infection
- Rural environment

Factors favoring the Th2 phenotype
- Widespread use of antibiotics
- Western lifestyle
- Urban environment
- Diet
- Sensitization to house-dust mites and cockroaches

Th1
Protective immunity

Th2
Cytokine balance

Allergic diseases including asthma
Hygiene hypothesis

Increased cleanliness in 20th century Western Society has led to greater number of allergic (Th2 skewed) individuals.

Protective exposures offered as evidence of the ‘Hygiene hypothesis’

- Older siblings  
  Strachan, BMJ 1989
- Lack of vaccination  
  Shirakawa, Science 1997
- Early life respiratory infections  
  von Mutius, E Resp J 1999
- Parasitic infection  
  Yazdanbaksh, Lancet 2000, Science 2004
- Day care attendance  
  Ball, NEJM 2000
- Gut microflora  
  Kalliomaki, Lancet 2001
- Animal exposure  
  Platts-Mills, Lancet 2001
- Consumption of unpasteurized milk  
  Riedler, Lancet 2001
- Exposure to a barn in the 1st year of life  
  Riedler, Lancet 2001
- Bacterial endotoxin  
  Braun Fahrlander, NEJM 2002
Protective effect of respiratory infections in infancy

• ≥2 episodes of “common cold” before age 1 yr decrease risk of asthma by age 7 by ~50%
• Other viral infections also protective
  • herpes
  • varicella
  • measles
• LRI with wheeze in the first 3 years of life increases risk of asthma

Illi S et al. BMJ. 322:390, 2001
Protective effect of early day care 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.

Asthma triggers
Allergens

- Small proteins (2-60 microns)
- Highly soluble
- Inhaled in dessicated particles (pollen grains, mite feces)
  - easily elute from the particle
  - diffuse into respiratory mucosa
- Enzymatically active (eg. proteases)
- Seasonal patterns of pollination:
  - Spring-trees
  - Summer-grass
  - Fall-ragweed
Viruses

Hospital admissions correlate with virus isolation peaks and school terms

Johnston et al. AJRCCM. 154:654, 1996
Johnston et. al. BMJ. 310:1225-1229, 1995
Nicholson et al. BMJ.;307:982, 1993
Viruses detected in adults hospitalized with asthma

N=33 organisms isolated

Immunopathogenesis
**Immunological mechanisms: Allergic sensitization**

- **APC** presents MHC Class II protein and epitope to **Naive T** cells.
- **Th2** cells produce IL-4 and IL-13, which activate **B** cells leading to the production of antigen-specific IgE.
- **Mast cell** degranulates upon binding antigen-specific IgE.
Immunological mechanisms: Reexposure

Immediate reaction

Late phase reaction

Mast cell

Mediator release

Th2

IL-4
IL-13
IL-5

Mucus production

Eosinophil
Counter-regulatory actions of the Th1 and Th2 pathways

**Th1 Pathway**
- IL-12
- IFN-γ
- TNF-β
- IL-2
- STAT1
- T-bet

**Th2 Pathway**
- IL-3
- IL-4
- IL-5
- IL-10
- IL-13
- STAT6, GATA-3, NFATc, c-maf

Interactions:
- IL-12 interacts with STAT1 and T-bet in the Th1 pathway.
- IFN-γ and IL-12 inhibit each other in both pathways.
- IL-4, IL-10, IL-13 inhibit STAT1 in the Th1 pathway.
- IL-4 inhibits STAT6 in the Th2 pathway.
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
Biomarkers

- IgE
- eNO
- Sputum eosinophilia
- Chitinase-like proteins

Asthma Subgroups
Occupational asthma

• "Variable airway narrowing causally related to exposure in the working environment to airborne dusts, gases, vapors or fumes"

• Two types
  • Specific IgE-mediated
  • Irritant induced (RADS)
Etiologies of occupational asthma: Low molecular weight chemicals

- Isocyanates (HDI, MDI, TDI)
- Woods (red cedar, exotic, sawmills)
- Glues (methacrylates, cyanoacrylates)
- Epoxies (anhydrides, amines)
- Colophony
- Dyes
Etiologies of occupational asthma
High molecular weight chemicals

- Flour - cereals
- Animal handling (dander)
- Latex
- Psyllium
- Crab processing
- Enzymes (eg. papain as meat tenderizer)
Exercise-induced asthma
Olympic gold medalists with asthma

And the entire 1988 U.S. water-polo team

DT, JJK, AS, TD
Exercise-induced asthma (EIA): Defn

• Self-limited syndrome of cough and/or wheezing, chest pain or chest tightness developing within 30 minutes of 2-8 minutes of continuous exercise or afterwards.

• Often reflection of the underlying asthma condition
Changes in pulmonary mechanics during and after exercise

Reproduced with permission
Pathogenesis

• Thermal hypothesis
  – cold air → ↑ blood flow to bronchial circulation
    → airway obstruction

• Osmotic hypothesis
  – cold dry air → in loss of fluid from the airway →
    hyperosmotic state → mast cell degranulation
    → releases bronchoconstrictive mediators
    → increases bronchovascular permeability

McFadden, ER. Allergy Principals and Practice (66):953-962. 1998
Sports specific factors

- Skaters: Ice resurfacing machines-emit PM’s

- Swimmers: inhaled chlorine (that produces nitrogen trichloride) can cause airway inflammation and lung epithelial hyperpermeability

Refractory Asthma: Types

• Severe despite appropriate therapy, vs
• Under-treated because of adherence or other problems
• “brittle” vs. nonbrittle
Airway remodeling

- Inflammation
- Mucus hypersecretion
- Subepithelial fibrosis
- Airway smooth muscle hypertrophy
- Angiogenesis
Refractory asthma: differential diagnosis

- Mild asthma with another functional breathing problem
- Stridor
- Persistent isolated cough
- Prolonged wheezing from bronchiolitis (infants)
- COPD
- LV Dysfunction
- VC Dysfunction (32% coexistent asthma)
Status asthmaticus

- An attack that continues for hours or even days without remission despite bronchodilator therapy
- Can be life-threatening
- May require mechanical ventilation
Asthma Management
### Targeted treatment of asthma

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Treatment</th>
<th>Allergen avoidance</th>
<th>Hypo-sensitization</th>
<th>Mast-cell stabilization: cromones, Isoprenaline, Omalizumab</th>
<th>Mediator antagonists: antihistamines, antileukotrienes</th>
<th>Late-phase inhibitors: steroids</th>
<th>Clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen</td>
<td>IgE synthesis</td>
<td>Mast cell degranulation</td>
<td>Inflammatory mediators</td>
<td>Allergic rhinitis</td>
<td>Asthma</td>
<td>Atopic eczema, urticaria</td>
<td>Food allergy</td>
</tr>
</tbody>
</table>

Adapted from Roitt J. Essential Immunology. 1994.
# NAEPP Classification of Asthma Severity

<table>
<thead>
<tr>
<th></th>
<th>Intermittent</th>
<th>Mild Persistent</th>
<th>Moderate Persistent</th>
<th>Severe Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms (days/week)</strong></td>
<td>&lt;2</td>
<td>&gt;2</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td><strong>Nighttime awakenings (times per month)</strong></td>
<td>&lt; 2</td>
<td>3-4</td>
<td>&gt;4</td>
<td>Often 7x/week</td>
</tr>
<tr>
<td><strong>FEV₁</strong></td>
<td>Normal</td>
<td>&gt;80% predicted</td>
<td>60 to 80%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td><strong>Initial Treatment Step</strong></td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
<td>Step 4 or 5</td>
</tr>
</tbody>
</table>
Updated 2007 NAEPP guidelines: 6 steps

- Step 1 - short acting inhaled beta agonist prn
- Step 2 - Low dose inhaled corticosteroid (ICS)
- Step 3 - Medium dose ICS or low dose ICS plus inhaled long acting beta agonist (LABA)
- Step 4 - Medium dose ICS plus LABA
- Step 5 - High dose ICS plus LABA
  - consider omalizumab (anti-IgE) therapy
- Step 6 - Oral corticosteroid
Omalizumab

- IgG1 kappa human framework containing murine antibody complementarity-determining regions (CDRs) (MW 150 kd)
- Humanized mAb against IgE (95% human)
- Binds circulating IgE regardless of specificity
- Does not activate complement
- Forms small, biologically inert omalizumab:IgE complexes

Adapted from Boushey H. *J Allergy Clin Immunol.* 2001;108:S77-S83
Omalizumab complexes bind free IgE and interrupts allergic cascade.
IgE receptors downregulated

$P = 0.0022$

High-risk patients

• Significant add-on therapy
  – Halves the number of asthma exacerbations
  – Reduces the likelihood of re-hospitalization

• Consistent reduction in exacerbation rates across all FEV\textsubscript{1} severity groups

• Greater improvements in lung function, asthma symptoms, and asthma-specific quality of life
Asthma Meds Under Scrutiny

- Pursuant to the 1987 Montreal Protocol, CFC propelled MDI off the marked and replaced with HFA ($, better?)
- 12/08: Large FDA hearing on the safety of LABAs:
  - SMART trial: increases in asthma-related deaths and life-threatening experiences in subjects treated with salmeterol vs placebo.
  - No requirement for concurrent treatment with inhaled ICS
  - supports the safety of LABAs when used with ICS
- 3/08; 1/09: FDA early communication about an ongoing safety review of montelukast in response to a possible association with behavior/mood changes, suicidality; incidence of suicidal ideation was less than 0.01%; no FDA conclusion yet
- 10/08: FDA early communication about increased risk for cardiovascular events in patients who received inhaled anticholinergic drugs (Tio); studies confounded by design; new update expected soon