Asthma

Don Hayes, Jr., MD, FAAP, FACP
Director, University of Kentucky Asthma Center
Kentucky Children’s Hospital
&
Assistant Professor of Pediatrics & Internal Medicine
University of Kentucky College of Medicine

Objectives

• Review the pathophysiology of asthma
• Review the prevalence of asthma
• Discuss diagnostic testing for asthma
• Discuss how to achieve asthma control
• Review aerosols used in asthma therapy
Asthma

• Asthma (Greek)
  – To breathe with open mouth or to pant
• Symptom or disease?
• Syndrome

So why wait? Rather than confusing scientists, doctors, and patients even further, is it not time to step out of the straightjacket of a seemingly unifying name that has outlived its usefulness? The conclusion should surely be that it is best to abolish the term asthma altogether. [Anonymous, Lancet 2006]

Definition of Asthma

• Bronchial hyperresponsiveness
• Airflow limitation (partially reversible)
• Airway inflammation induced by multiple mediators
• Bronchial smooth muscle spasm & hypertrophy
• ↑ mucus production
• Persistent or intermittent symptoms
  – Wheezing, cough, SOB, & chest tightness

1995 NHLBI/WHO Workshop Report
Bronchoconstriction

Before

10 Minutes After Allergen Challenge

The Development of Asthma

Genetic Tendency

Allergens → Smoke → Ozone → ASTHMA

Bacteria

Endotoxins

Viruses
The Hygiene Hypothesis

Birth

Many infections (T\(_{H1}\) stimuli)
Farm animal exposure

Only child
Few infections

No allergies
T\(_{H1}\)

Allergies
Still T\(_{H2}\)

Allergic Diseases & Autoimmune Diseases are Rising

Bach, NEJM 2002;347:911-20
Longitudinal Evaluation of Lung Function in Wheezing Infants

• Risk Factors:
  – Mothers with asthma
  – Atopy
    • Elevated IgE at 9 months
    • Positive skin tests
    • Eczema
    • Allergic Rhinitis
    • Eosinophilia
  – Wheezing at times other than infection
  – ? Viruses

Martinez et al, NEJM 1995;332:133-8

Asthma Predictive Index

History of \( \geq 4 \) wheezing episodes in the past year (at least one must be physician diagnosed)

\[ \text{PLUS} \]

<table>
<thead>
<tr>
<th>One major criteria</th>
<th>or</th>
<th>Two minor criteria</th>
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</thead>
<tbody>
<tr>
<td>Parent with asthma</td>
<td></td>
<td>Food sensitivity</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td></td>
<td>Peripheral eosinophilia ((\geq 4%))</td>
</tr>
<tr>
<td>Aeroallergen</td>
<td></td>
<td>Wheezing not related to infection</td>
</tr>
</tbody>
</table>

If +, then 65% likelihood of developing clinical asthma
If -, then 95% likelihood of not developing clinical asthma

Factors Influencing Asthma Development & Expression

Host Factors
- Genetic
- Gender
- Obesity

Environmental Factors
- Indoor allergens
- Outdoor allergens
- Occupational sensitizers
- Tobacco smoke
- Air Pollution
- Respiratory Infections
- Diet

Burden of Asthma

- WHO
  - Asthma is one of the most common chronic diseases worldwide
    - Most common chronic disease in children
  - Estimated 300 million affected individuals
  - Prevalence ↑ in many countries
  - Mortality → highest in lower income countries
- US annual data
  - 134 million days of restricted activity
  - 14 million days of lost school days
  - ~ 500,000 hospitalizations
  - ~ 5000 deaths
Epidemiology in the US

- 14 million adults → asthma
- 9 million children → asthma
- 4 million US children had an asthma attack in the past year
- Disparity between black & white non-Hispanic children → ↑
- Asthma morbidity & mortality → ↑


Source: MMWR
Asthma Prevalence
United States, 1980-2004

Source: National Health Interview Survey; National Center for Health Statistics

Asthma Mortality:
Mild Patients Are Also at Risk

Diagnosing Asthma

• Clinical diagnosis
  – Historical, physical & laboratory findings
    • History of episodic symptoms of airflow obstruction
      – Cough
      – Chest tightness
      – Dyspnea
    • Physical: wheeze, hyperinflation
    • Laboratory: spirometry, exhaled nitric oxide (eNO)
    • Chest x-ray
  – Exclude other possibilities
Differential Diagnosis of Asthma

- Allergic rhinitis & post nasal drip
- Chronic sinusitis
- Gastroesophageal reflux
- Obstruction of the large airways
  - Laryngotraceomalacia
  - Enlarged tonsils
  - Foreign body aspiration
  - Vocal cord dysfunction
  - Vascular ring, subglottic stenosis, congenital lesions of the airway
- Obstruction of the small airways
  - Cystic fibrosis
  - Bronchopulmonary dysplasia
  - Bronchiolitis obliterans
  - Bronchectasis & COPD
- Heart disease

Diagnosing Asthma

- Objective measures
  - Spirometric evidence of obstruction
    - Reduced FEV₁/FVC ratio
  - Spirometric evidence of reversibility
    - FEV₁ increase of >12%
    - FEV₁ increase of ≥200 mL
  - Challenge Tests
    - Exercise
    - Methacholine
    - Cold air
    - ? hot/humid air challenge
Spirometry

<table>
<thead>
<tr>
<th>Spirometry (BTPS)</th>
<th>PRED</th>
<th>PRE-RX</th>
<th>POST-RX</th>
<th>% CHG</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (Liters)</td>
<td>4.47</td>
<td>4.30</td>
<td>96</td>
<td>4.33</td>
</tr>
<tr>
<td>FEV1 (Liters)</td>
<td>3.88</td>
<td>2.76</td>
<td>72</td>
<td>3.38</td>
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<tr>
<td>FEV1/FVC %</td>
<td>86</td>
<td>64</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>FEV50-75% LVEF</td>
<td>4.31</td>
<td>1.65</td>
<td>28</td>
<td>3.02</td>
</tr>
<tr>
<td>PEF (Liters)</td>
<td>5.19</td>
<td>7.03</td>
<td>86</td>
<td>7.43</td>
</tr>
<tr>
<td>FVC (Liters)</td>
<td>4.47</td>
<td>6.13</td>
<td>9</td>
<td>0.09</td>
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</tbody>
</table>

Levels of eNO in asthma

Treatment

Environmental Control Measures

• Tobacco smoke
• Allergens
  – Dust mites
  – Animals
  – Cockroaches
  – Pollens
  – Mold
• Strong odors, chemicals
• Medications
Drug Therapy of Asthma

**Rescue Medication**
- Short acting β₂ agonists
- Anti-cholinergic agents
- Systemic corticosteroids

**Controllers**
- Inhaled corticosteroids
- Leukotriene modifiers
- Long-acting β₂ agonists
- Cromolyn & Nedocromil
- Theophylline
- Omalizumab (Anti-IgE)

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**Short-acting β₂-Agonists**

- Most effective drug for relief of bronchospasm
- Use only as needed
- Frequent use = poor asthma control
- Adverse effects
  - Tachycardia
  - Tremors
  - Headache
  - Insomnia
- Levalbuterol (Xopenex®) may be an option for patients who experience side effects
Levalbuterol (Xopenex®)

- R Isomer of albuterol
- Does not contain S Isomer
- Effective bronchodilation at half the dose
- Longer duration of action
- Decreased side effects, better tolerated
- Now available as solution & MDI
- More expensive than albuterol

Systemic Corticosteroids

- Indicated for exacerbations
- Short-term “burst” therapy
  - Usually → 3 to 10 days
- No evidence to suggest that tapering dose after improvement ↓ the risk of relapse
- Short-term adverse effects
  - Abnormalities of glucose metabolism
  - Increased appetite, fluid retention
  - Peptic ulcer
  - Mood alteration
Inhaled Corticosteroids

- Most effective long-term control medication
- Safe when use is monitored
- ↓ Asthma symptoms
  - Bronchial hyperreactivity
  - Exacerbations & hospitalizations
  - Need for rescue medications
- ↑ pulmonary function
- Improves quality of life
- ↓ hospitalizations
- ↓ mortality

ICS – Finding the Right Balance

The range that the risk:benefit ratio is favorable is that at which the wanted effects in the lungs increases steeply with dose while the unwanted systemic effects increase gradually. At higher doses, the increase in risk greatly outweighs the slight remaining increase in benefit. This relationship seems to vary for different inhaled corticosteroids.

Barnes et al, Am J Respir Crit Care Med 1998;157:S1-S53
Mean Annual Increase in FEV$_1$ During Inhaled Steroid Therapy

Asthma Duration at Start of ICS Therapy (Yrs)*

*Mean values and 95% confidence intervals are shown.

Agertoft & Pedersen, Respir Med 1994;88:373-81

Preventing Early Asthma in Kids: The PEAK Trial

Guilbert et al, NEJM 2006;354:1985-97
ICS Use Lowers Risk of Death from Asthma

Suissa et al, NEJM 2000; 343: 332-336

Low Dose ICS Impacted Growth

- Average height %tile
  - End of Treatment
    ICS: 51.5%ile
    Placebo: 56.4%ile
    \( p = 0.0001 \)
  - End of observation
    ICS: 54.4%ile
    Placebo: 56.4%ile
    \( p=0.03 \)
- Height growth over 3 years
  - Mean \( \uparrow \) in height from baseline in fluticasone group
    - 1.1 cm < placebo group
      - End of 24 month Rx period
    - 0.7 cm < placebo group
      - End of the observation year

Guilbert et al, NEJM 2006;354:1985-97
Growth Velocity & Asthma Control

Ninan et al, Arch Dis Child 1992;67:703-705

ICS vs. Montelukast

Busse et al, J Allergy Clin Immunol 2001;107:461-468
ICS Are More Effective at Decreasing Asthma Exacerbations Than Anti-leukotriene Agents

Results not affected by type of medication, methods, analysis, publication status or funding source. Insufficient evidence in children.

* No exacerbations reported

Ducharme, BMJ 2003;326:621

Salmeterol & ICS vs. Montelukast & ICS

MDI vs. Nebulizer

Lung Deposition in the Same Subject

HFA = hydrofluoroalkane  CFC = chlorofluorocarbon

Leach et al, Chest 2002;122:510-516
Leach et al, Am J Respir Crit Care Med 2000;161(3):A34

The clinical efficacy of radiolabeled deposition imaging is unknown.
Particle Size & Airway Deposition

- **Particle Size**
  - > 5 microns
  - 2-5 microns
  - < 2 microns

- **Result**
  - No clinical benefit
  - Systemic absorption if swallowed
  - Optimal size for clinical benefit
  - Clinical benefit uncertain

Effect of Particle Size on Lung Function in Patients With Asthma

Adapted from Rees et al, *Eur J Respir Dis Suppl* 1982;63:73-78

* P<0.05 compared with baseline

Terbutaline administered to 10 patients with asthma via MDI.
Mean Absolute Improvement of Percent Predicted FEV$_1$ from Baseline

- Albuterol Via:
  - Nebulizer
  - High dose MDI
  - Low dose MDI

% Change in FEV$_1$

Time (min) 0 30 60 90

$P=0.12$ for all treatment groups


MDI

- Variability of dose
  - Factors
    - System related bias
      - Human factor
      - ↓ with spacers, masks
MDI

• Advantages
  – Portable
  – No power needed
  – Minimal maintenance
  – Less cooperation
    • Face mask for infants & children
    • Spacer for all others

MDI + Spacer

• Advantages of spacer
  – ↓ velocity & size of aerosol particles
  – ↓ need for accurate coordination
    • Actuation & inspiration
  – Large particles impact spacer & sediment
  – Propellant evaporates in the spacer
Nebulizer

- Size of particle is variable (2-10 microns)
  - Variable based on compressor pressure-flow
  - Intrinsic nebulizer features: design, volume fill, dynamic flow
  - Environmental factors (temp, humidity)
  - Inhalation flow
  - Solution or suspension of drug
  - Viscosity, density, surface tension of drug

Nebulizer - Disadvantages

- Time consuming (10-12 min)
- Bulky & maintenance
- Power
- Cost
- Noisy (50-70 dB)
- Erratic drug targeting
  - Compressor pressure-flow
  - Mask
  - Oropharyngeal deposition
    - 5-10%, up to 66% of inhaled dose
MDI vs. DPI

- Metered dose inhalers (MDIs)
  - Needs spacer with mask or mouthpiece
  - Spacer ↓ required coordinated inhalation
    - Infants & younger children
  - Need to take more inhalations
- Dry powder inhalers (DPIs)
  - Need to be able to coordinate inhalation
  - Need to understand the use of different techniques with different medications

Education

- Critical
  - Optimizing adherence
  - Recognizing exacerbations
- Teaching done
  - Physicians
  - Nurses/NP
  - Respiratory therapists
- Important impact on prevention of exacerbations
- Plan of action for exacerbations
Conclusions

• Asthma is a major burden for the US
• Correct diagnosis of asthma is imperative
• Asthma therapy should be individualized
• Corticosteroids → crucial for treatment
  – Inhaled
    • Nebulizer & compressor
    • MDI with spacer
    • DPI
  – Oral
• Choose method aerosol to provide best delivery & compliance → optimal control
• Asthma education is critical

"Mr. Osborne, may I be excused? My brain is full."