Asthma

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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 straitjacket 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. ■ The Lancet

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

Allergens
Smoke
Ozone

Genetic Tendency

Bacteria
Endotoxins
Viruses

ASTHMA
The Hygiene Hypothesis

- **Birth**: TH2
- **Many infections (TH1 stimuli)**
- **Farm animal exposure**
- **Birth**: TH2
- **Only child**
- **Few infections**
- **No allergies**
- **TH1**
- **Allergies**
- **Still TH2**
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)

PLUS

One major criteria or Two minor criteria

- Parent with asthma
- Atopic dermatitis
- Aeroallergen sensitivity
- Food sensitivity
- Peripheral eosinophilia ($\geq 4\%$)
- Wheezing not related to infection

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

## Factors Influencing Asthma Development & Expression

<table>
<thead>
<tr>
<th>Host Factors</th>
<th>Environmental Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Indoor allergens</td>
</tr>
<tr>
<td>Gender</td>
<td>Outdoor allergens</td>
</tr>
<tr>
<td>Obesity</td>
<td>Occupational sensitizers</td>
</tr>
<tr>
<td></td>
<td>Tobacco smoke</td>
</tr>
<tr>
<td></td>
<td>Air Pollution</td>
</tr>
<tr>
<td></td>
<td>Respiratory Infections</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
</tr>
</tbody>
</table>
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

Asthma Deaths by Age per 1,000,000 Children 1980 - 1998

Source: National Vital Statistics System, NCHS, CDC
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
  - Laryngotracheomalacia
  - 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
  - Bronchiectasis & 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

![Graph showing spirometry results]

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>(BTPS)</th>
<th>PRED</th>
<th>PRE-RX BEST</th>
<th>%PRED</th>
<th>POST-RX BEST</th>
<th>%PRED</th>
<th>% CHG</th>
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<tr>
<td>FVC</td>
<td>Liters</td>
<td>4.47</td>
<td>4.30</td>
<td>96</td>
<td>4.33</td>
<td>97</td>
<td>1</td>
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<tr>
<td>FEV1</td>
<td>Liters</td>
<td>3.85</td>
<td>2.76</td>
<td>72</td>
<td>3.38</td>
<td>88</td>
<td>22</td>
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<tr>
<td>FEV1/FVC</td>
<td>%</td>
<td>86</td>
<td>64</td>
<td>72</td>
<td>78</td>
<td>88</td>
<td>22</td>
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<tr>
<td>FEF25-75% L/sec</td>
<td></td>
<td>4.31</td>
<td>1.65</td>
<td>38</td>
<td>3.03</td>
<td>70</td>
<td>84</td>
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<tr>
<td>PEF</td>
<td>L/sec</td>
<td>8.19</td>
<td>7.03</td>
<td>86</td>
<td>7.43</td>
<td>91</td>
<td>6</td>
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<td>FIVC</td>
<td>Liters</td>
<td>4.47</td>
<td>0.13</td>
<td>3</td>
<td>0.05</td>
<td>1</td>
<td>-63</td>
</tr>
</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)
Short-acting $\beta_2$-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
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 FEV₁ 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

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 \( R_x \) period
    - 0.7 cm < placebo group
      - End of the observation year

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
The clinical efficacy of radiolabeled deposition imaging is unknown.

Leach et al, *Chest* 2002;122:510-516
Particle Size & Airway Deposition

Particle Size

> 5 microns
No clinical benefit
Systemic absorption if swallowed

2-5 microns
Optimal size for clinical benefit

< 2 microns
Clinical benefit uncertain
Effect of Particle Size on Lung Function in Patients With Asthma

![Graph showing the effect of particle size on lung function].

- *<5 µm*
- 5-10 µm
- 10-15 µm

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


$P=0.12$ for all treatment groups
• 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
ASTHMA

Home Management Plan of Care (HMPC) for: ________________________________

Your child has a follow up appointment with ________________________________
on._____________________(day)____________________(date)
at _____________ a.m./p.m.

The contact number for your appointment is ( ) ______________________

Triggers to avoid that could cause MY asthma attack

My child’s asthma attack (circle all that apply)

- Tobacco smoke
- Exercise
- Food
- Dust
- Cleaning products
- Cockroaches
- Animal dander
- Mold/Mildew
- Pollen
- Aerosol sprays
- Perfume
- Strong smells
- Weather conditions
- Stress
- Other: _______________________

I have been educated about asthma by the following:

- Video
- Asthma Education Book
- Written
- Verbal
- Demonstration

I have been educated about quitting smoking and on the dangers of second-hand smoke.

Child Parent

I have reviewed the asthma education material provided by Kentucky Children’s Hospital, and I am able to state the signs, symptoms, and triggers of an asthma attack.

Child Parent

For more information on asthma or other health topics please visit:

http://medlineplus.gov/

*This document has been modified from Dayton Children’s Hospital Asthma Action Plan with permission.

Top copy to patient Copy to chart
Asthma Action Plan for: ____________________________

**My Asthma is in Good Control**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>How much to take</th>
<th>When to take</th>
</tr>
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<tbody>
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**Daily Medicines - use EVERYDAY**

- Breathing is good
- No cough or wheeze
- Can work/play
- Sleeps at night

20 minutes before sports, use this medication:

**Peak flow in this area (most of the time):** __________ to __________

**My Asthma is only Partially Controlled**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>How much to take</th>
<th>When to take</th>
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**Daily Medicines plus add these Quick Relief Medicines**

- Cough
- Wheeze
- Tight chest
- Wakes up at night

Call the doctor if quick relief medicine is used more than two (2) times a week.

**Peak flow in this area (most of the time):** __________ to __________

**My Asthma is Uncontrolled**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>How much to take</th>
<th>When to take</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

**Take these Medicines**

- Medicine not helping
- Breathing hard & fast
- Nose opens wide
- Can't walk/talk well
- Ribs show

**Peak flow below:** __________

1, the physician, have reviewed and agree with the Action Plan __________ Date __________

(Patient name and initial)

Call 911 If...

- child's lips are bluish
- breathing is getting worse fast
- can't talk or cry because of hard breathing
- struggling to breathe
- has passed out

Specialist Provider Name: ____________________________ Phone: ____________________________

Primary Care Provider Name: ____________________________ Phone: ____________________________

Home Management Plan of Care Reviewed by: ____________________________ Date: ____________

Parent/Guardian signature: ____________________________ Date: ____________

Patient signature: ____________________________ Date: ____________

(if patient can read)
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.”