Pediatric Asthma:
The Old the New and Hopefully
Not the Blue

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KEY OBJECTIVES:

- Review the unique characteristics of infancy and the infant airway predisposing to wheezing
- Identify clinical conditions that mimic asthma in children
- Recognize the importance of atopy and early infection in the development of persistent wheezing
Asthma Facts

14.9 Million Persons
1.5 Million ED Visits
500,000 Hospitalizations
Over 5,500 Deaths
Disproportionately Affects Children
Costs of Asthma: $11.3 Billion
The Nature of the Beast

- **Most common chronic illness in childhood**
  - 87% had unscheduled physician visits in the year prior to hospitalization

- **#1 chronic illness causing school absences**
  - 3X the school absences of children without asthma

- **78% of parents report a negative impact on the entire family**
  - 40% of patients have sleep disturbance
    - 1-2 nights/week
  - 36% of parents reported missing work due to their child’s asthma in the prior year
Hospitalizations Due to Asthma in Children

Differential Diagnoses:
Remember all that wheezes is not ASTHMA

PEDIATRICS
- Infection - VIRAL (RSV)
- Asthma
- Anatomic Abnormalities
  - Malacia
  - TEF
  - Vascular ring/sling
  - Mediastinal mass/tumor
  - CAMs, cysts, CLE, sequestration
  - Congenital Heart Disease (L→R shunt)
- Inherited - CF and Immunodeficiency
- BPD
- Aspiration - GERD, FB
- ILD including BO
- VCD

ADULTS
- VCD
- Asthma
- COPD
- Congestive Heart Failure
- Anatomic - Airway tumor, LAD
- Bronchiectasis
- ILD including BO
<table>
<thead>
<tr>
<th></th>
<th>Pathophysiologic Properties Predisposing Infants and Young Children to Wheeze</th>
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<tbody>
<tr>
<td>1.</td>
<td>↓ Bronchial smooth muscle content</td>
</tr>
<tr>
<td>2.</td>
<td>Hyperplasia of bronchial mucous glands</td>
</tr>
<tr>
<td>3.</td>
<td>↓ radius of conducting airways</td>
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<tr>
<td>4.</td>
<td>↑ peripheral airway resistance due to ↓ size</td>
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<td>5.</td>
<td>↑ Chest wall compliance</td>
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<td>6.</td>
<td>Diaphragm</td>
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<td>- Horizontal insertion of the diaphragm to the rib cage</td>
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<tr>
<td></td>
<td>- ↓ number of fatigue-resistant skeletal muscle fibers</td>
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<tr>
<td>7.</td>
<td>Deficient collateral ventilation</td>
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Asthma: Definition

- Symptoms of recurrent wheezing, dyspnea, chest tightness and/or cough
- Classic triad of:
  - Bronchoconstriction
    - Airflow obstruction, variable and often reversible
    - 12% and >200 ml increase in FEV$_1$
    - Bronchial hyperactivity
      - Worsening with exposure to various stimuli
      - Methacholine sensitivity – most common
      - Cold air sensitivity – particularly in young children
  - Mucous Hypersecretion
  - Chronic airway inflammation
Pathogenesis of Asthma

Genetics

Environmental Factors
- Respiratory Infection
- Smoking (maternal)
- Western Lifestyle
- Antibiotic use
- Allergens
- Obesity
- Inner City
- Pollution

Gene-by-environment interaction

Asthma
Bronchoconstriction

Before

10 Minutes After Allergen Challenge
Airway Mucosal Edema
Inflammatory Mediators and Asthma

- Mast cells
- Macrophages
- Eosinophils
- T-lymphocytes
- Epithelial cells
- Platelets
- Neutrophils
- Myofibroblasts
- Basophils

Mediator Soup

- Bronchoconstriction
- Microvascular leak
- Mucous secretion
- Airway hyperresponsiveness

Histamine
- Lipid mediators
- Peptides
- Cytokines
- Growth factors
Bronchial Biopsy From Subjects With and Without Asthma - The Role of Inflammation

Normal

Asthma
Asthma Pathophysiology

Acute response
- Bronchial hyperreactivity
- Mucosal edema
- Airway secretions

Chronic inflammatory response
- Increased inflammatory cell numbers
- Epithelial damage
Airway Remodeling

Expiration Volume

Inspiration Flow

Expiration Volume

Inspiration Flow

Inflammation
Asthma Treatment in CO children ages 1-14, 2011

Source: Colorado Health and Hospital Association
Relative Risk of Hospitalization in the United States

Rate of Decline in FEV₁

<table>
<thead>
<tr>
<th>Age - Years</th>
<th>Normals (n=186)</th>
<th>Asthmatic patients (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>20</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>40</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>60</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>80</td>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Adapted from Peat. Eur J Respir Dis. 1987;70:17.
“Thank God! A panel of experts!”
The Natural History of Asthma

Genetic Factors (Atopy)

Virtuses

Wheezing

Allergens

Family hx asthma
Passive smoke exposure
Atopic disease

Inflammation and Remodeling

Persistent asthma & irreversibly reduced FEV₁
Longitudinal Evaluation of Lung Function in Wheezing Infants

Martinez FD et al. NEJM 332:133, 1995
Bronchial Asthma in Infants

• Early diagnosis is difficult
  – Reactive airway disease
  – Viral induced wheeze

• Features of disease are less clear

• To date, clinical diagnosis in infancy relies on a h/o:
  – ≥ 3 episodes of wheezing (≥1 MD dx)
  – Coexistence of atopy or a specific trigger
Fetal Development and the Immune System

- **Pregnancy = TH\(_2\) state**
  - Allergen specific IgE can be detected in cord blood
  - Cord blood cells can proliferate in response to allergen by 22 weeks gestation
  - Placenta produces increased amounts of TH2 cytokines (IL-4, -5, and -10)

Wheezing in Young Children is a Significant Problem

- **Peak incidence: 2-5 months of age**
  - >60% will have wheezed
  - 50% will have at least 2 or more episodes of wheezing
  - 40% who wheeze in the first 3 years of life will continue to wheeze at 6 years of age

- **Up to 50% of pediatric hospital admissions during the winter are due to wheezing**

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Asthma Phenotypes
Infant Wheezing: Phenotypes

- Distinguishing factors:
  - Atopy
  - Airway Hyperresponsiveness
  - Lung Function
Asthma Predictive Index

H/o ≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)

PLUS

- One major criteria or
  - Parent with asthma
  - Atopic dermatitis
  - Aeroallergen sensitivity

- Two minor criteria
  - Food sensitivity
  - Peripheral eosinophilia (≥4%)
  - Wheezing not related to infection

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

Eczema at 2 years of age

Source: Joseph Spahn, MD, National Health, Denver, Colorado.
Child with chronic cough with positive skin test reactions to common Aeroallergens.

Source: Joseph Spahn, MD, National Jewish Health, Denver, Colorado.
Presentation of Allergic Rhinitis: Clues

- Nasal itching
- Repeated nose rubbing ("allergic salute")
- Mouth breathing
- Allergic shiners

The Effects of AI
Perennial Allergen Sensitization Early in Life & Chronic Asthma In Children

- **German Multicenter Allergy Study (MAS)**
  - birth cohort of 1314 children
  - followed from birth to 13 yrs
    - Sensitization measured at 1,2,3,5,6,7, &10 yrs;
    - Allergen exposure at 6 &18 mo, 3, 4, 5 yrs;
    - Lung function at 7, 10, 13 yrs.

- **Results:**
  - 90% with recurrent wheeze but not atopic had lost their symptoms at school age and had normal lung function at 13yrs
  - 56% atopic wheezers had active asthma at 13 yrs.
  - Sensitization to indoor allergens ≤ 3 yrs associated with impaired lung function

Illi et al., Lancet 2006; 368:763-70.
Time of Sensitization and Exposure: Lung Function Impairment at 7 yrs

Illi et al., Lancet 2006; 368:763-70.
Infantile Wheeze - AHR

- Infants are born with highly responsive airways becoming less so with age.
  - Factors such as parental smoking, respiratory illness and/or allergen exposure predispose infants to airway narrowing and potential decline in lung function.
  - These factors may interfere with the natural decline in airway hyperresponsiveness with age progression.
Airway Hyperresponsiveness in Infancy

- Independent of other risk factors assessed (or other physiologic indices), increased airway responsiveness to histamine at 1 month of age was significantly associated at age 6 yrs with the following:
  - Decreased FEV$_1$ (p<0.001)
  - Decreased FVC (p<0.001)
  - MD-diagnosed asthma (p<0.001)
  - Lower respiratory tract symptoms (p<0.05)

Transient Early Wheezing

- Characterized by recurrent episodes of wheezing in the first year of life
  - Resolution of symptoms between ages 3-5 years\(^1\)
- Most prevalent form of early wheezing
  - Almost 60% of subjects who wheezed in TCRS had resolution of their symptoms by age 6\(^1\)

- No significant relationship to atopy\(^1,2\)
- No significant findings of AHR

Transient Wheezers

- **Risk factors:**
  - Maternal smoking during pregnancy
    - Only significant variable associated in TCRS (OR 2.2 [95% CI 1.3-3.7])\(^1\)
    - Italian Studies of Respiratory Disorders in Childhood and the Environment (SIDRIA; OR 1.46 [95% CI 1.26-1.69])\(^2\)
    - Swedish BAMSE cohort (4089 infants); OR 2.1 [95% CI 1.2-3.7]\(^3\)
  - Lower level of lung function in infancy before any respiratory infections\(^4\)

\(^3\)Lannero E et al. Respir Res 2006; 7:3.
Prenatal Influences in Asthma

- *In utero* exposure to cigarette smoke increases BHR

- Conclusion: Mothers should avoid known allergens and tobacco smoke during pregnancy

ARRD. 1988;138:518.
BAL Cells in Wheezing Children (WC) Compared to Normal Controls (NC)

Cells x 10^4/ml

Krawiec ME; AJRCCM 163:1338, 2001
Childhood Asthma is Characterized by AW Eosinophilia while Infantile Wheezing Characterized by AW Neutrophilia

Marguet; AJRCCM 159:1553, 1999
The Role of Infection
Viruses

Wheezing Illnesses

Resolution or Transient Wheezing

Persistent Wheezing or ASTHMA
Asthma Risk Factors: Respiratory Illness

Healthy Infant

RSV
PIV
RV
MPV
Chlamydia

Wheezing Illness

Resolution

Atopy

Asthma

Acute Exacerbation

RV
MPV
Mycoplasma

Does the age at which the first moderate to severe infection occurs differ among the three wheezing phenotypes?

100% Viral Recovery by 1 yr

p < 0.0001
Life would be infinitely happier if we could only be born at the age of eighty and gradually approach eighteen.........

Mark Twain
Thank you for your attention!!!!!!