Allergic Inflammation in Infant/Preschool Wheezing

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Disclosures

- Speaker’s Bureau: Aerocrine
KEY OBJECTIVES:

- Review the unique characteristics of infancy and the infant airway predisposing to wheezing
- Review the phenotypic presentations of early childhood wheezing
- Recognize the importance of atopy and early infection in the development of persistent wheezing
- Identify biomarkers which may distinguish transient from persistent wheezing children
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

Pathophysiologic Properties Predisposing Infants and Young Children to Wheeze

1. ↓ Bronchial smooth muscle content
2. Hyperplasia of bronchial mucous glands
3. ↓ radius of conducting airways
4. ↑ peripheral airway resistance due to ↓ size
5. ↑ Chest wall compliance
6. Diaphragm
   - Horizontal insertion of the diaphragm to the rib cage
   - ↓ number of fatigue-resistant skeletal muscle fibers
7. Deficient collateral ventilation
Bronchoconstriction

Before

10 Minutes After Allergen Challenge
Airway Mucosal Edema
Airway Remodeling

Inflammation

Expiration

Volume

Inspiration

Flow

Expiration

Volume

Inspiration

Flow
Medication Use and Asthma Severity

Asthma in America™ Survey
“Thank God! A panel of experts!”
The Natural History of Asthma

Genetic Factors (Atopy)

Viruses

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
Infant Wheezeing: Phenotypes

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

- History of ≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)

**PLUS**

- **One major criteria** or **Two minor criteria**
  - Parent with asthma
  - Atopic dermatitis
  - Aeroallergen sensitivity
  - 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
Child with chronic cough with positive skin test reactions to common aeroallergens.
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.
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\(^1,2\)

Transient Wheezers

**Risk factors:**

- **Maternal smoking during pregnancy**
  - Only significant variable associated in TCRS (OR 2.2 [95% CI 1.3-3.7])
  - Italian Studies of Respiratory Disorders in Childhood and the Environment (SIDRIA; OR 1.46 [95% CI 1.26-1.69])
  - Swedish BAMSE cohort (4089 infants); OR 2.1 [95% CI 1.2-3.7]

- Lower level of lung function in infancy before any respiratory infections

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The Effects of Atopy
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 13 yrs.
  - 56% atopic wheezers had active asthma at 13 yrs.
  - Sensitization to indoor allergens \( \leq 3 \) yrs associated with impaired lung function

Time of Sensitization and Degree of Exposure Determines Degree of Lung Function Impairment at 7 yrs

Asthma Histopathology in Children

- **Lung biopsies** from 2 children with asthma in remission compared to 2 children dying in status
  - **Similar:** Goblet cell hyperplasia, mucus plugging, collagen deposition
  - **Different:** In status, larger numbers of submucosal eosinophils and more extensive denudation of the epithelium

Bronchial Biopsy From Subjects With and Without Asthma

Normal

Asthma
Add EM slide of patient with asthma
Jonathan Malka, 5/9/2009
The Epithelium and Pediatric Asthma

- Bronchial specimens post mortem or by bronchoscopy and biopsy in children 5-15 years
  - 7 nonasthmatics
  - 7 moderate asthmatics
  - 9 severe asthmatic

Federov IA et al. Thorax 2005; 60:389-394
Bronchoscopy and Bronchoalveolar Lavage

BAL Cells 48 h After Allergen Challenge

Laboratory of Drs. Jarjour and Kelly.
Inflammation in Wheezing Infants

- Infants and children < 60 mos with prolonged wheezing (> 2 mos within a 6 month period) not responding to conventional therapy
  - Exclusion:
    - Acutely wheezing
    - > 450 µg/day of ICS
    - receiving antibiotics, oral steroids, or LTRAs within 1 mo of evaluation

- BAL of right middle lobe
- Data on patients with + bacterial cultures or elevated LI was not included in the final analyses

BAL Cells in Wheezing Children (WC) Compared to Normal Controls (NC)

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
Sputum


60 asthmatic children
27 NC

Fractional Exhaled Nitric Oxide

Niox MINO®
What is exhaled nitric oxide also known as the fractional exhaled nitric oxide (FeNO)?

- Bronchial epithelium produces NO and its fraction in exhaled air
  - elevated in atopic asthma
  - a biomarker of eosinophilic allergic airway
  - FeNO is a biomarker which reacts rapidly in response to treatment or worsening of the disease

- Normal levels have now been established for children (20-25 ppb).
  - <20 ppb – unlikely to benefit from ICS therapy
  - 20-35ppb – may respond; evaluate in clinical context
  - >35 ppb – likely to response from ICS therapy
Why is knowing the exhaled NO helpful in allergic asthma?

- Measuring FeNO helps:
  - Identify steroid-responsive inflammation
  - Predicts and assess the patient’s response to ICS anti-inflammatory therapy
  - May help optimize the dosage of ICS treatment
  - May help to predict loss of control and possible relapse therefore improving asthma outcomes
  - Helpful in monitoring compliance to ICS

eNO as a Predictor of Asthma Exacerbation in Young Children during ICS Reduction

N=40
30 tolerated 1 dose reduction
12 weaned off
6 loss of asthma control

eNO Off-Line Tidal Breathing Collection System
Life would be infinitely happier if we could only be born at the age of eighty and gradually approach eighteen........

Mark Twain