

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



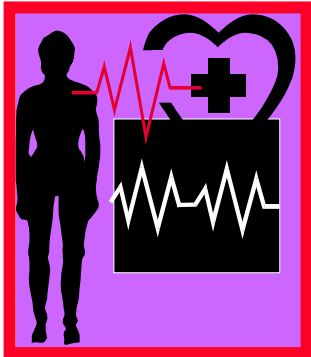
14.9 Million Persons



1.5 Million ED Visits



500,000
Hospitalizations



Over 5,500 Deaths



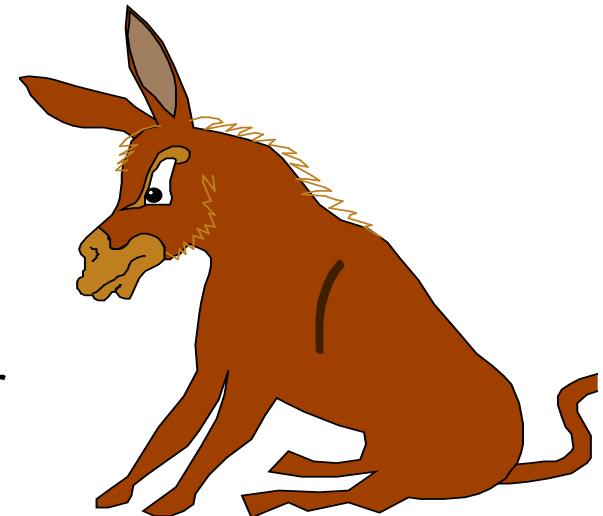
Disproportionately Affects Children



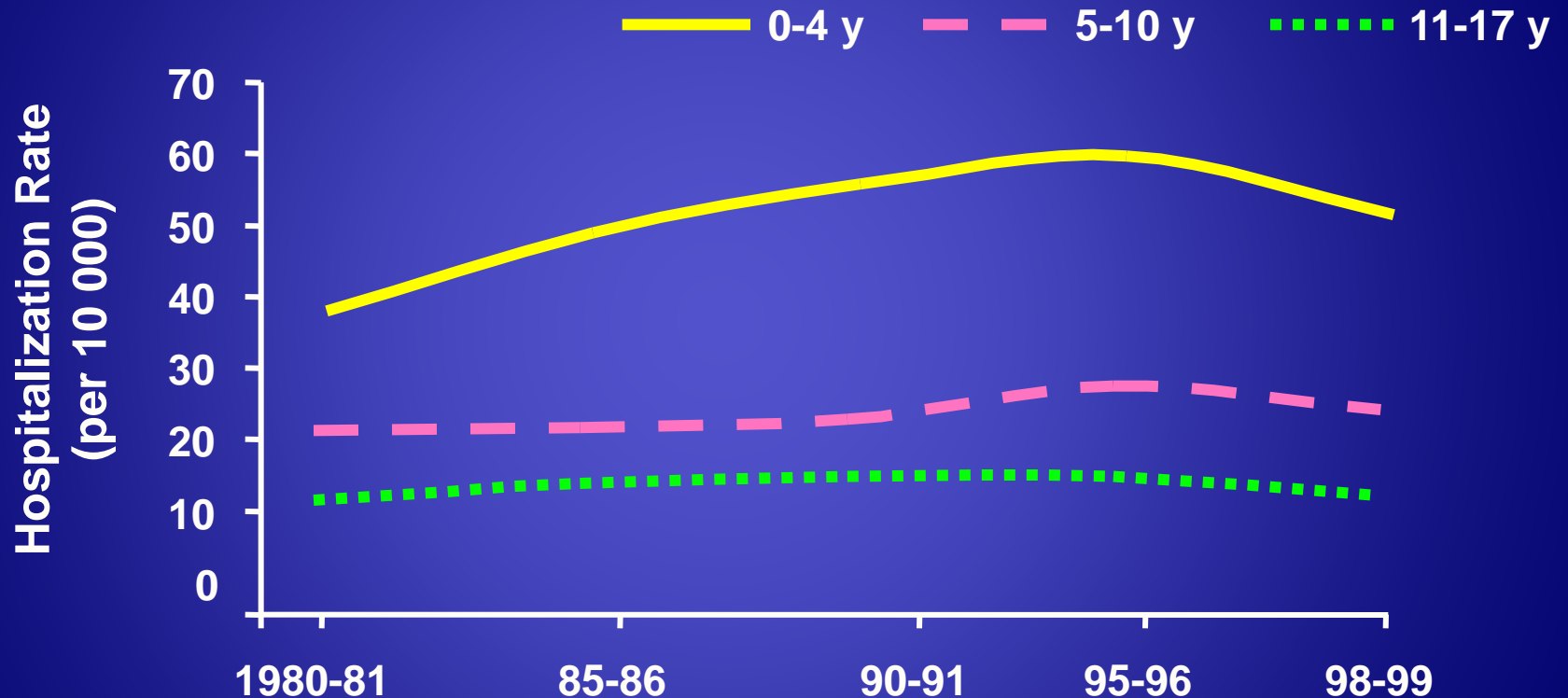
Costs of Asthma
\$11.3 Billion

The Nature of the Beast

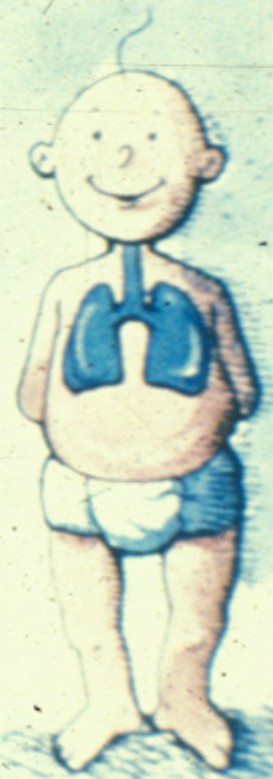
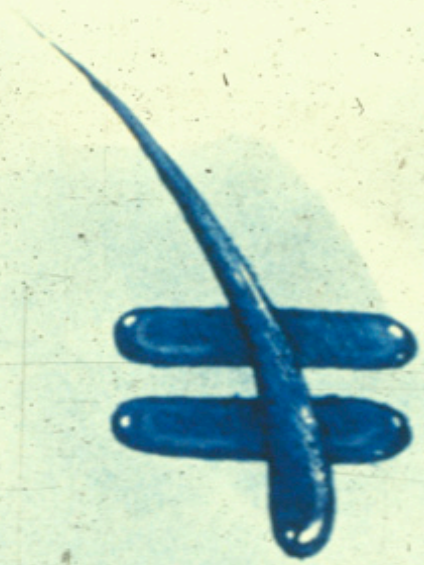
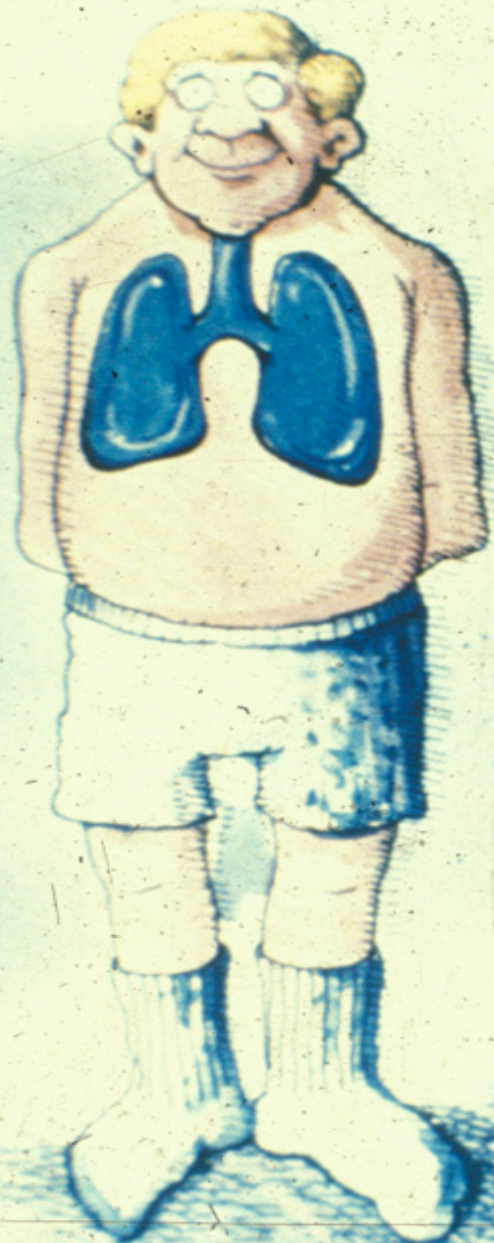
- **Most common chronic illness in childhood**
 - 87% had unscheduled physician visits in the year prior to hospitalization
- **#1 chronic illness causing school absences**
 - 3X the school absences of children without asthma
- **78% of parents report a negative impact on the entire family**
 - 40% of 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



Akinbami and Schoendorf. *Pediatrics*. 2002;110:315-22.



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**

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

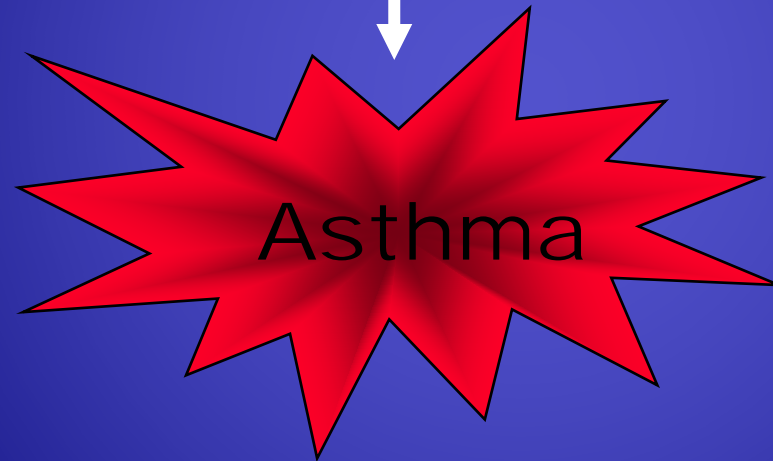
Asthma: Definition

- **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 FEV₁**
 - **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

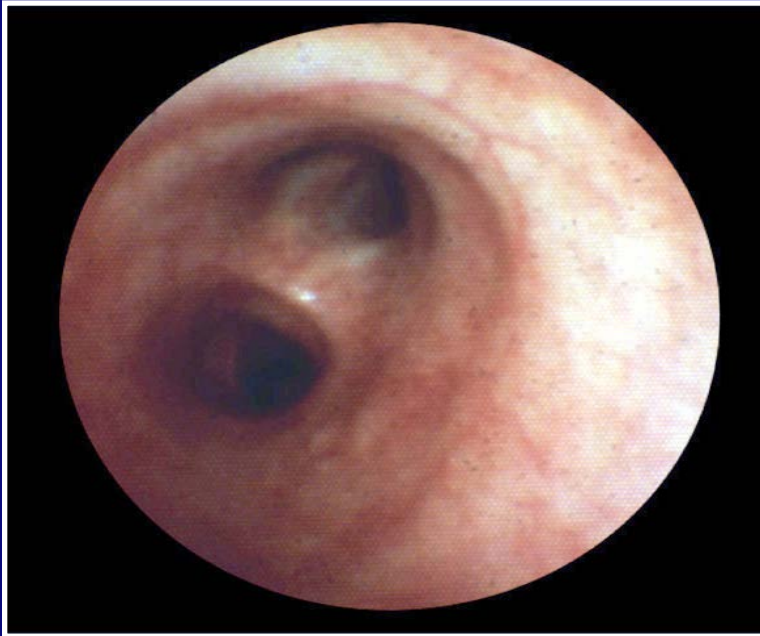
Environmental Factors



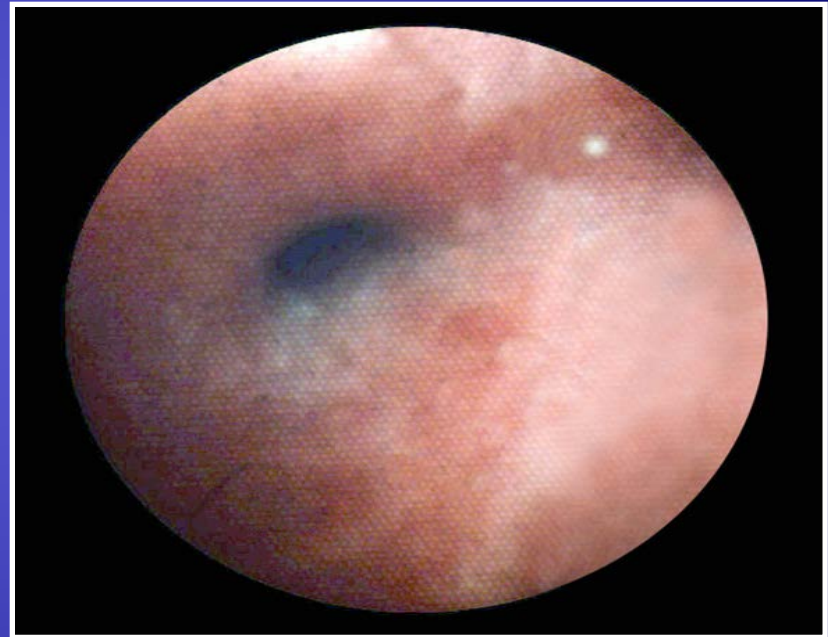
- Respiratory Infection
- Smoking (maternal)
- Western Lifestyle
- Antibiotic use
- Allergens
- Obesity
- Inner City
- Pollution

Gene-by-environment interaction

Bronchoconstriction

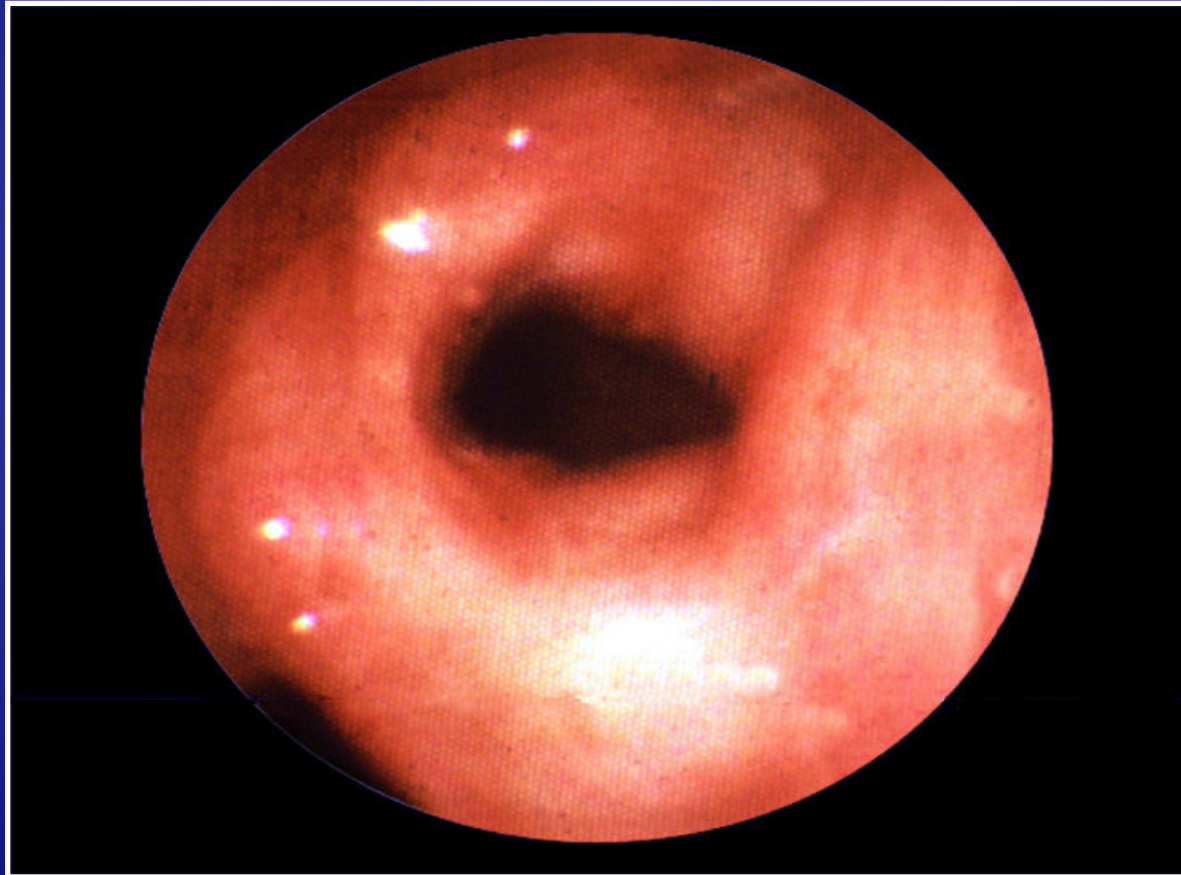


Before

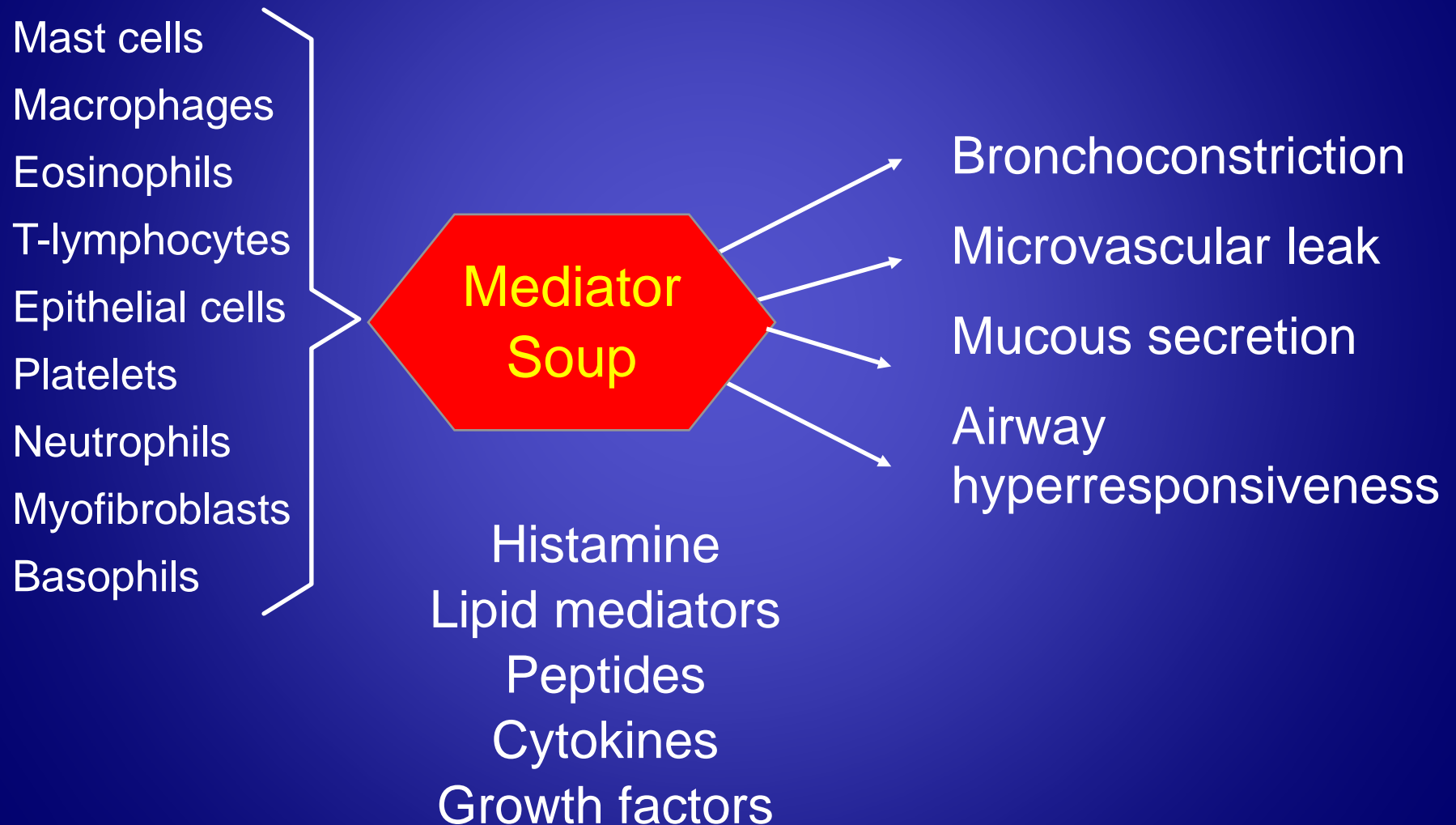


**10 Minutes After
Allergen Challenge**

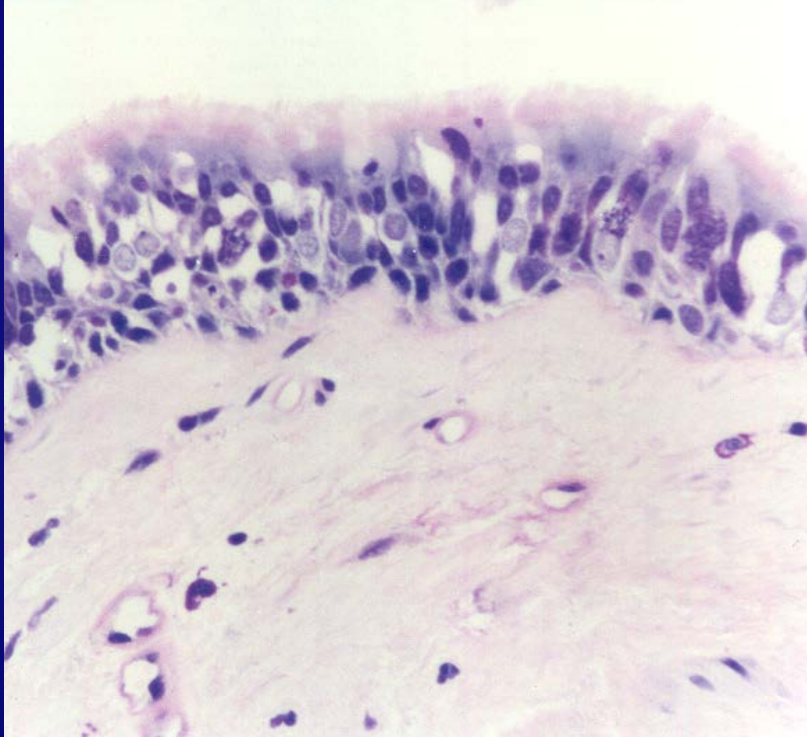
Airway Mucosal Edema



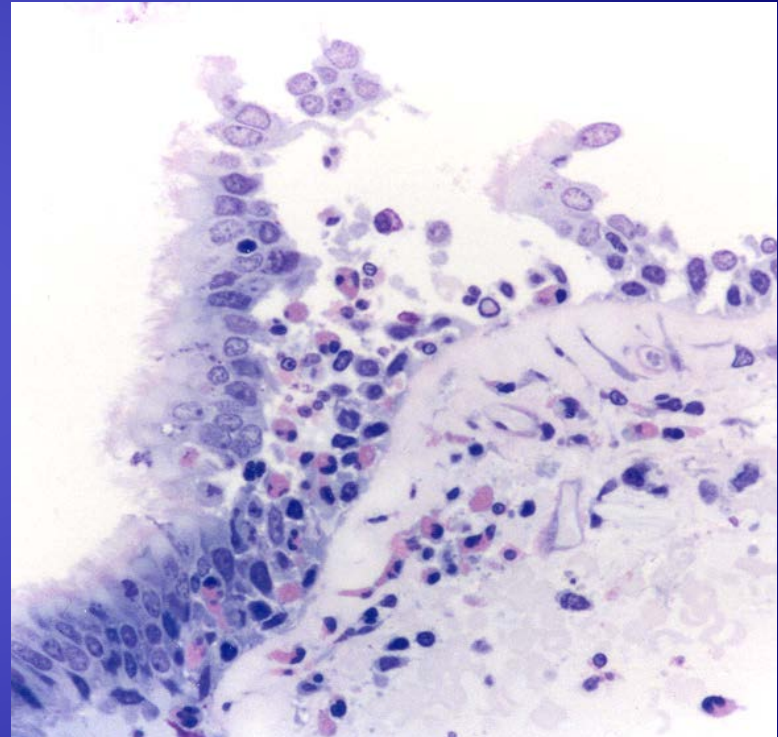
Inflammatory Mediators and Asthma



Bronchial Biopsy From Subjects With and Without Asthma -The Role of Inflammation

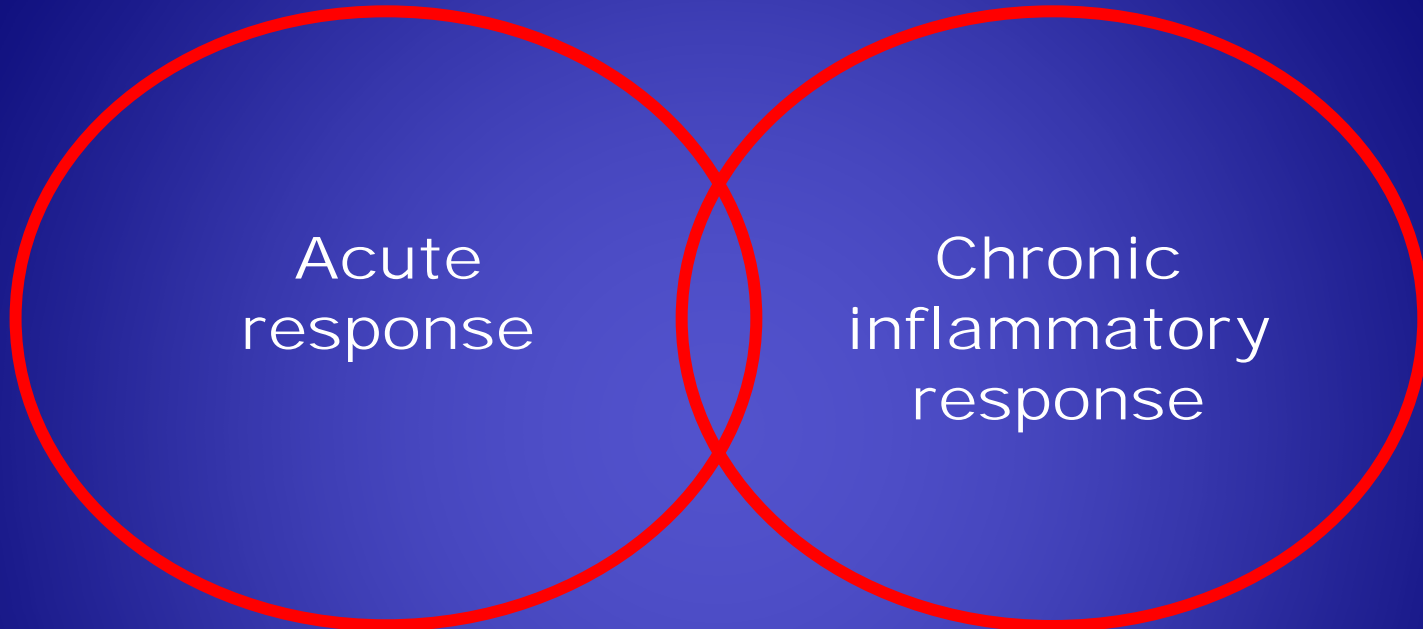


Normal



Asthma

Asthma Pathophysiology



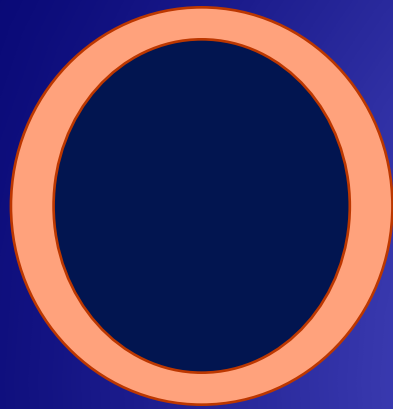
Acute
response

Chronic
inflammatory
response

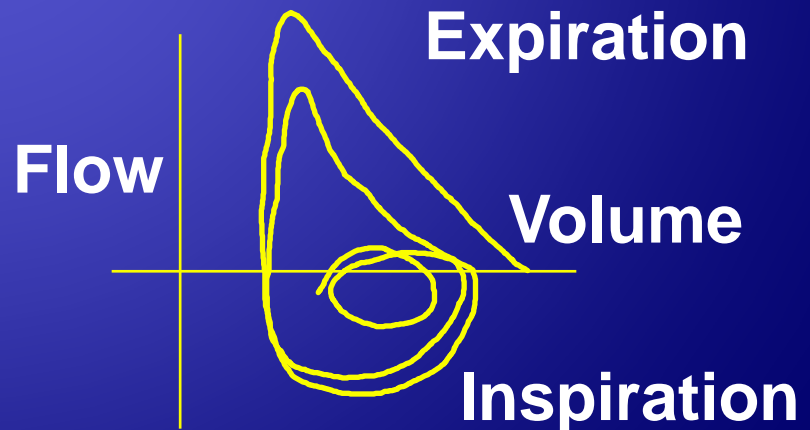
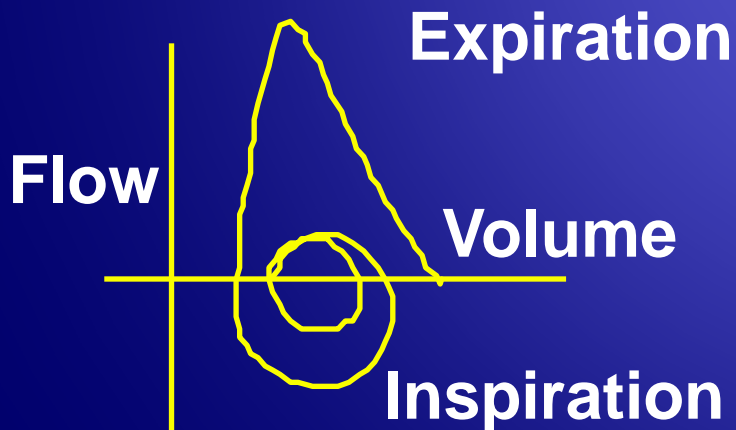
- **Bronchial hyperreactivity**
- **Mucosal edema**
- **Airway secretions**

- **Increased inflammatory cell numbers**
- **Epithelial damage**

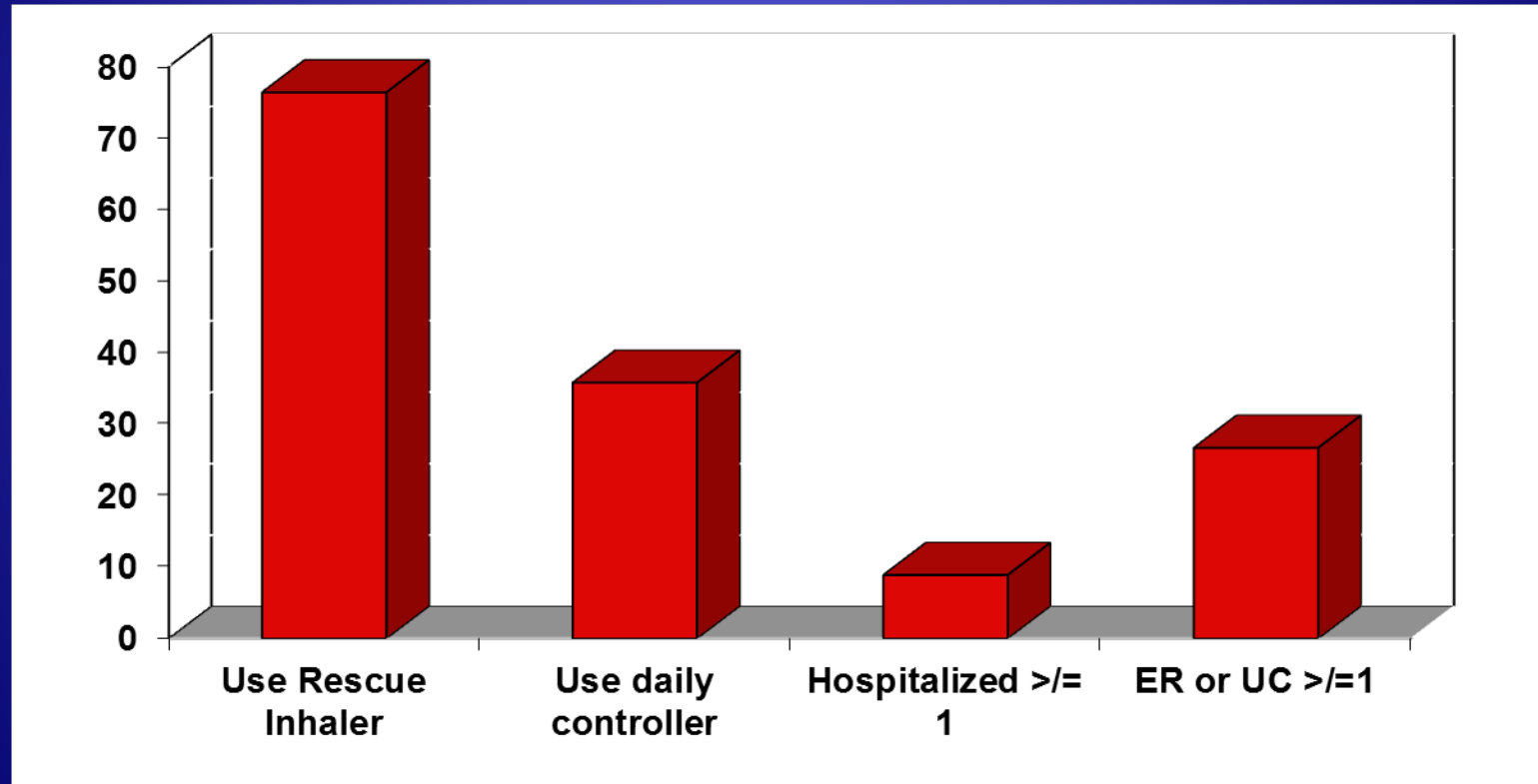
Airway Remodeling



Inflammation

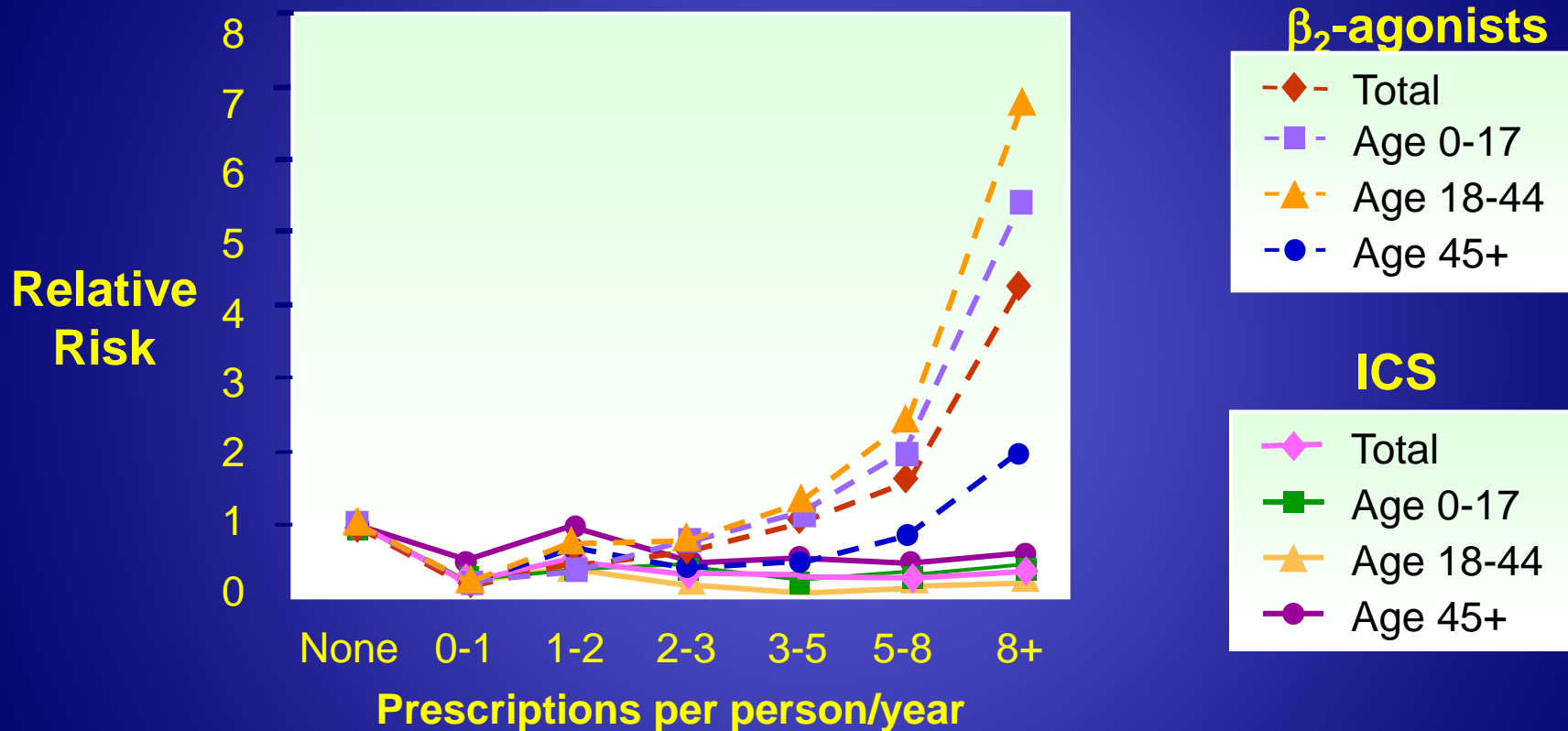


Asthma Treatment in CO children ages 1-14, 2011



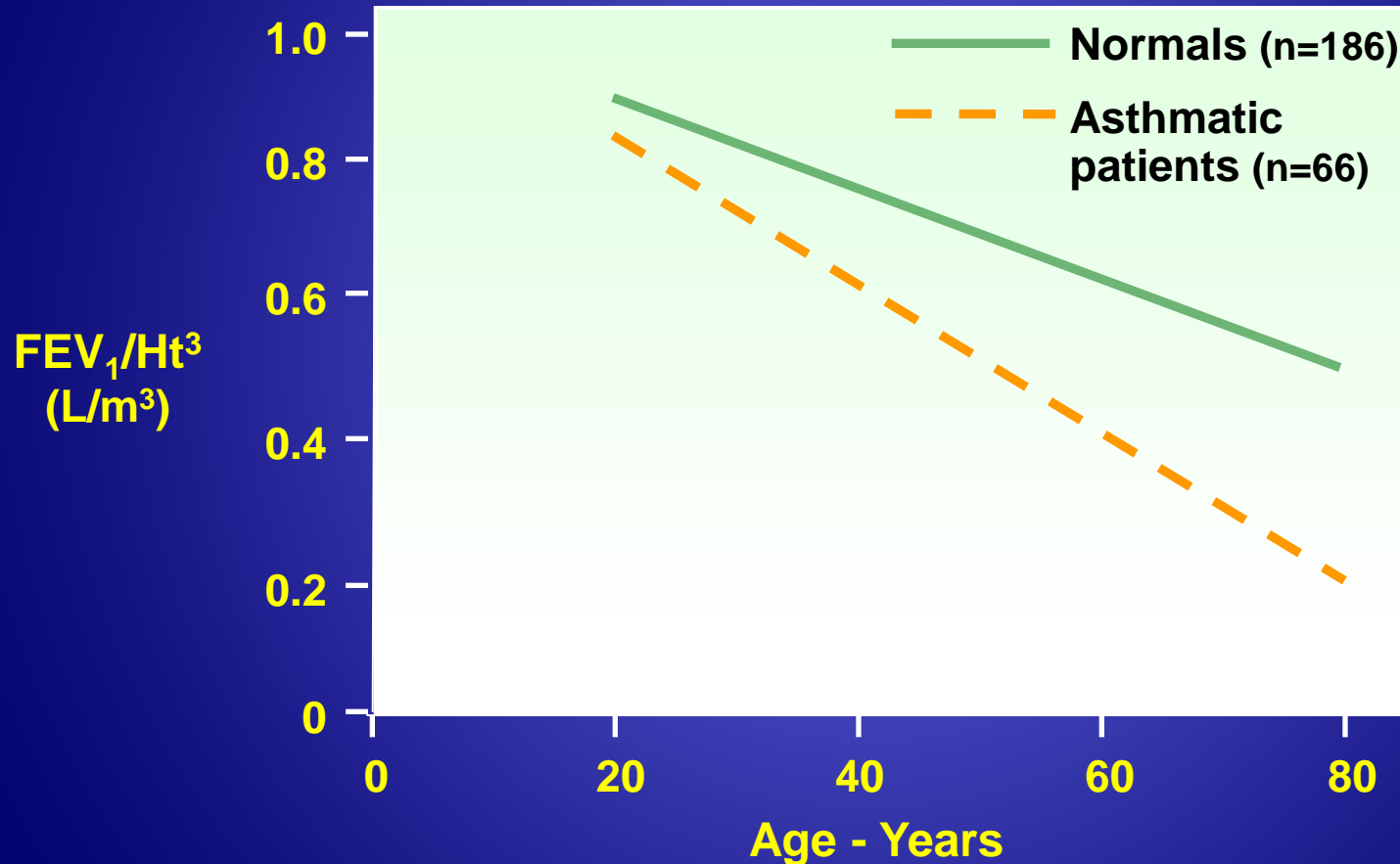
Source: Colorado Health and Hospital Association

Relative Risk of Hospitalization in the United States



Donahue J, et al. JAMA. 1997;277:887-891.

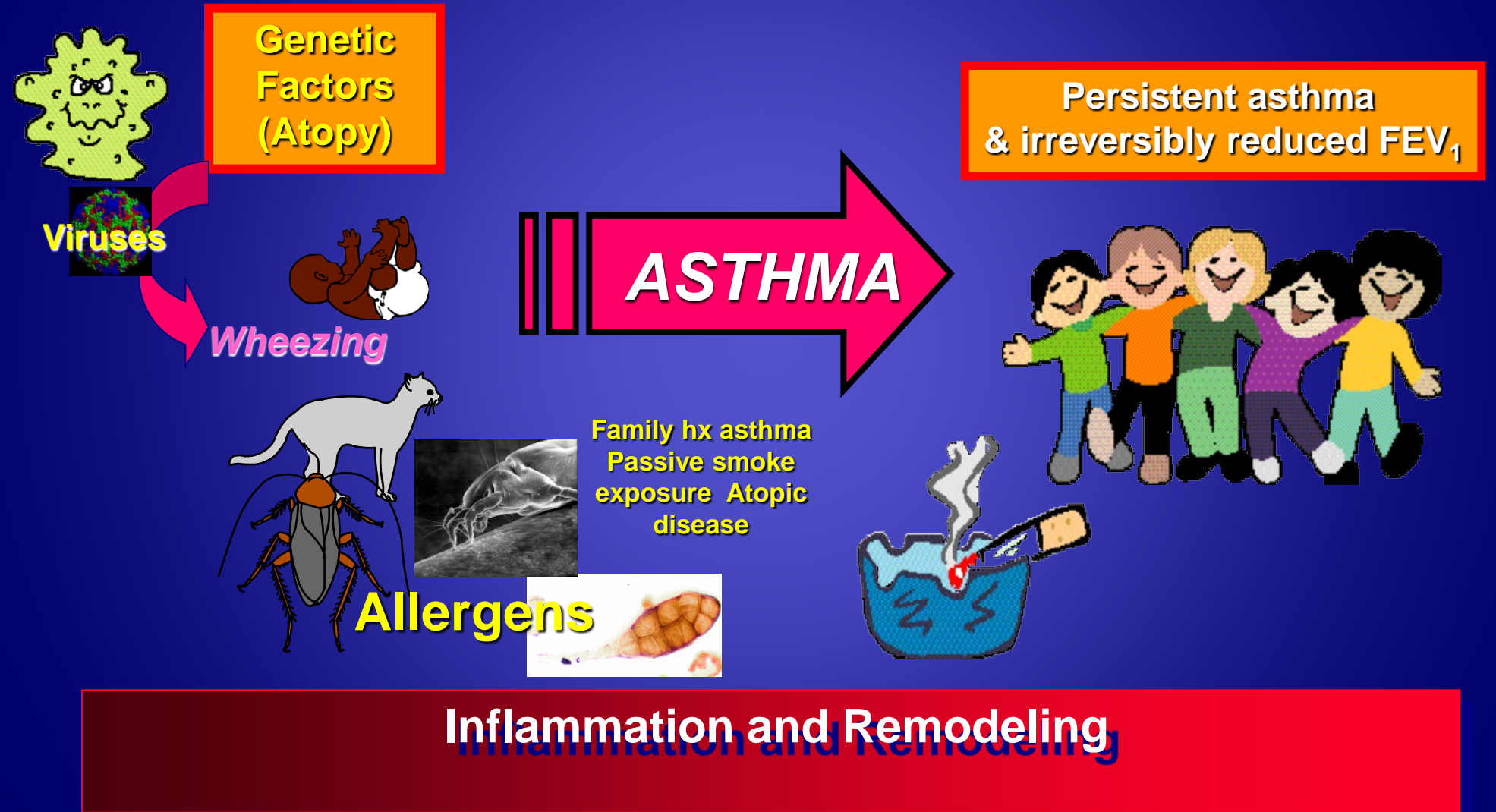
Rate of Decline in FEV₁



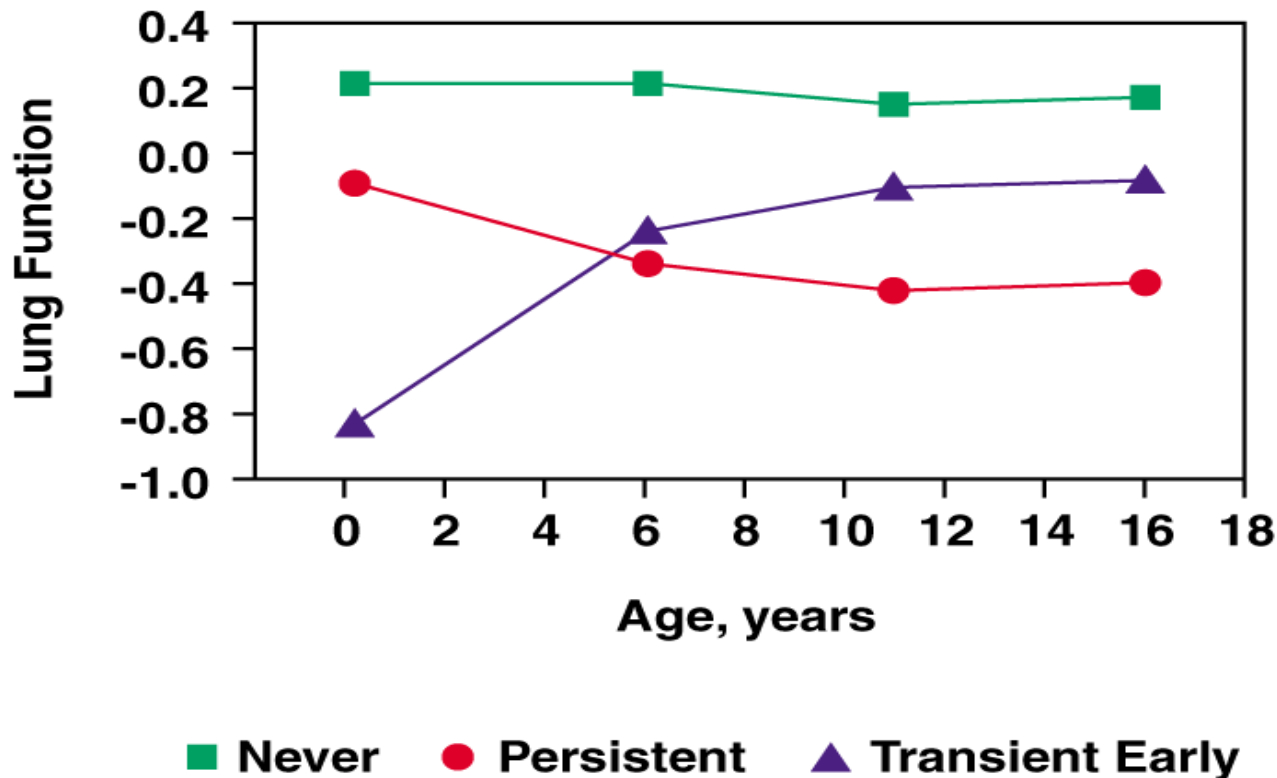


"Thank God! A panel of experts!"

The Natural History of Asthma



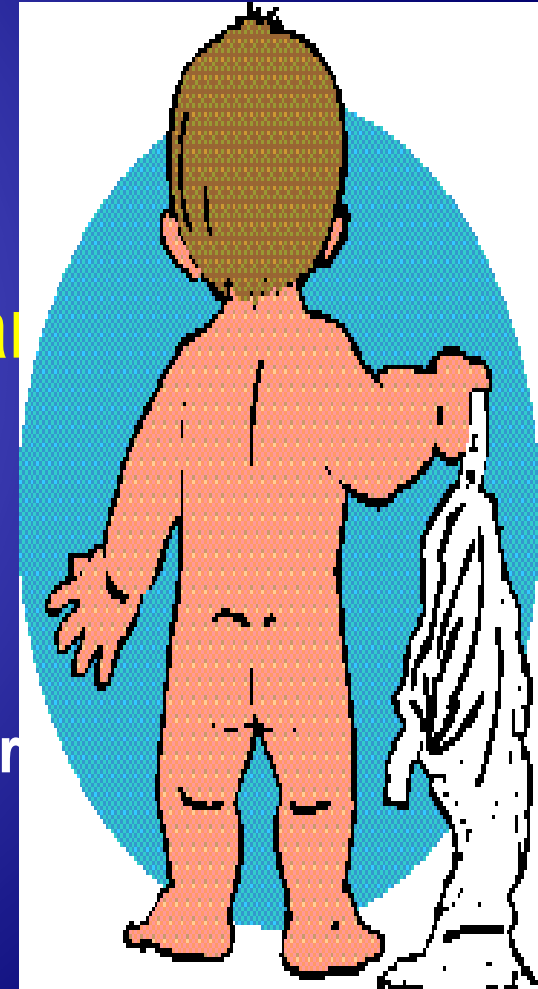
Longitudinal Evaluation of Lung Function in Wheezing Infants



Martinez FD et al. *NEJM* 332:133, 1995

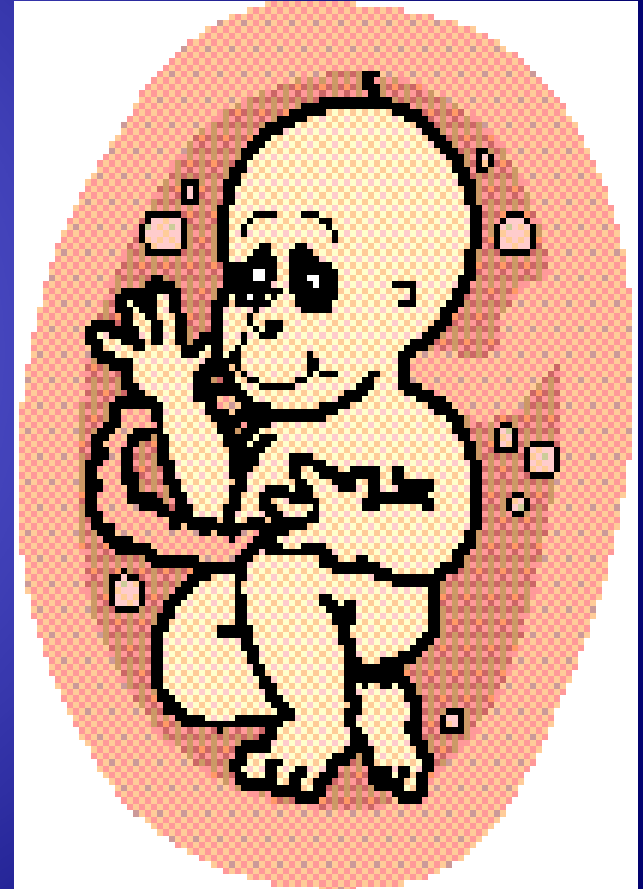
Bronchial Asthma in Infants

- **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 = TH₂ 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 age¹**
 - >60% will have wheezed
 - 50% will have at least 2 or more episodes of wheezing²
 - 40% who wheeze in the first 3 years of life will continue to wheeze at 6 years of age³
- **Up to 50% of pediatric hospital admissions during the winter are due to wheezing⁵**

¹Holberg CJ, et al. Am J Epidemiol 1991; 133:1135-51.

²Martinez FD, Godfrey S: Wheezing Disorders in the Preschool Child. 2003

³Martinez FD, et al. N Engl J Med 1995; 332: 133-8.

⁴Tager IB, et al. Am Rev Respir Dis 1993; 147: 811-7.

⁵Wilson NM. Clin Exp Allergy 1994; 24: 522-29.

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 -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

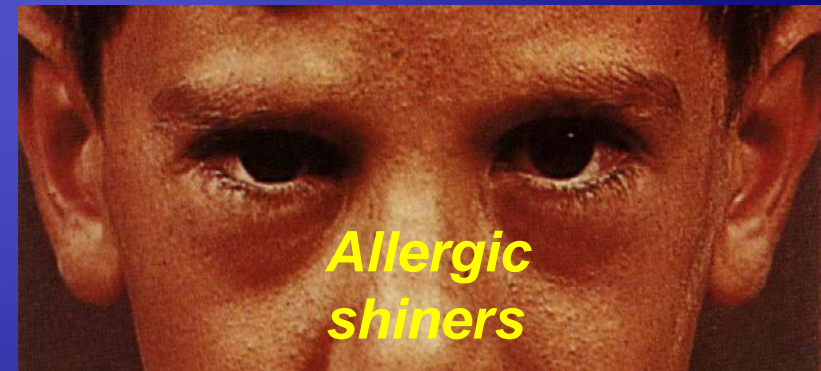
Eczema at 2 years of age



Child with chronic cough With Positive Skin Test Reactions to Common Aeroallergens



Presentation of Allergic Rhinitis: Clues



Reprinted from: Skoner D, Urbach A, Fireman P.
In: Atlas of Pediatric Physical Diagnosis. 3rd ed. 1997:(chap 4).
By permission of the publisher Mosby.

The BEETS

OF ADOPT

Perennial Allergen Sensitization Early in Life & Chronic Asthma In Children

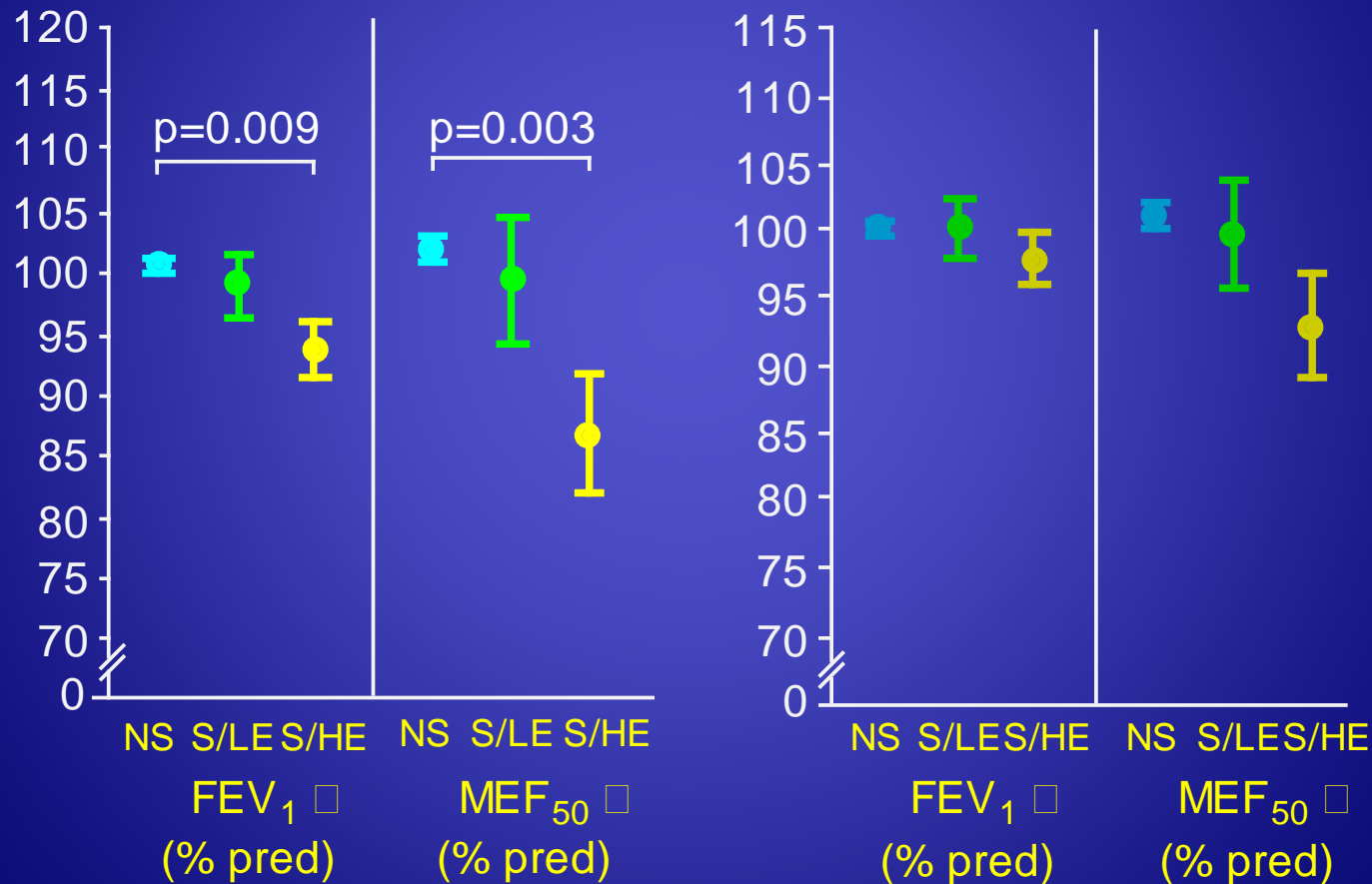
- **German Multicenter Allergy Study (MAS)**

- 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 \leq 3 yrs associated with impaired lung function

Time of Sensitization and Exposure: Lung Function Impairment at 7 yrs



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 FEV₁ (p<0.001)
 - Decreased FVC (p<0.001)
 - MD-diagnosed asthma (p<0.001)
 - Lower respiratory tract symptoms (p<0.05)

Transient Wheeler

Transient Early Wheezing

- Characterized by recurrent episodes of wheezing in the first year of life
 - Resolution of symptoms between ages 3-5 years¹
- Most prevalent form of early wheezing
 - Almost 60% of subjects who wheezed in TCRS had resolution of their symptoms by age 6¹
- No significant relationship to atopy^{1,2}
- No significant findings of AHR

¹Martinez FD, et al. N Engl J Med 1995; 332: 133-8.

²Kurukulaaratchy RJ, et al. Clin Exp Allergy 2003; 33: 573-78.

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

¹Stein RT, et al. Am J Epidemiol 1999; 149: 1030-7.

²Rusconi F, et al. Am J Respir Crit Care Med 1999; 160: 1617-22.

³Lannero E et al. Respir Res 2006; 7:3.

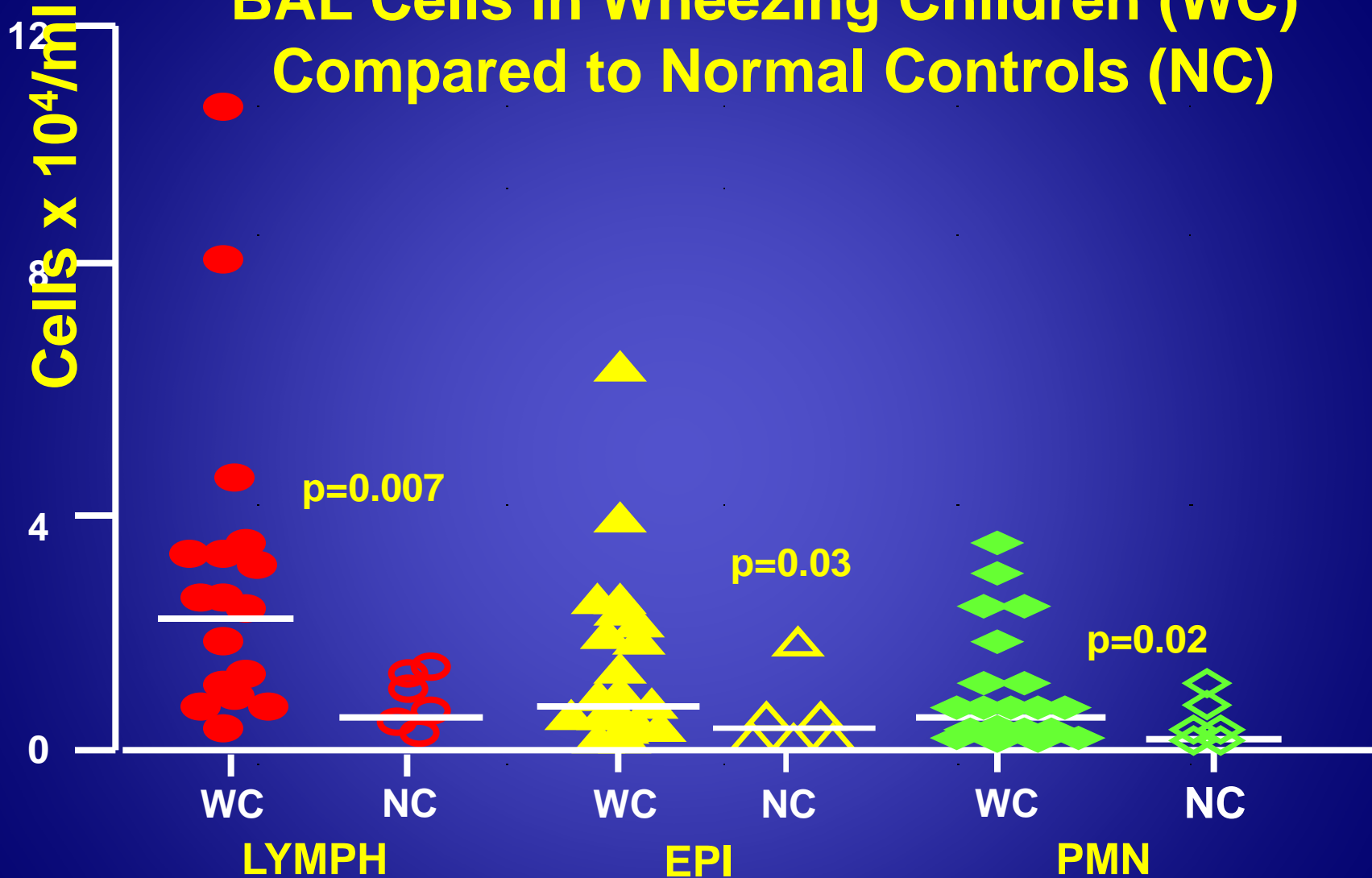
⁴Martinez FD, et al. N Engl J Med 1995; 332: 133-8.

Prenatal Influences In Asthma

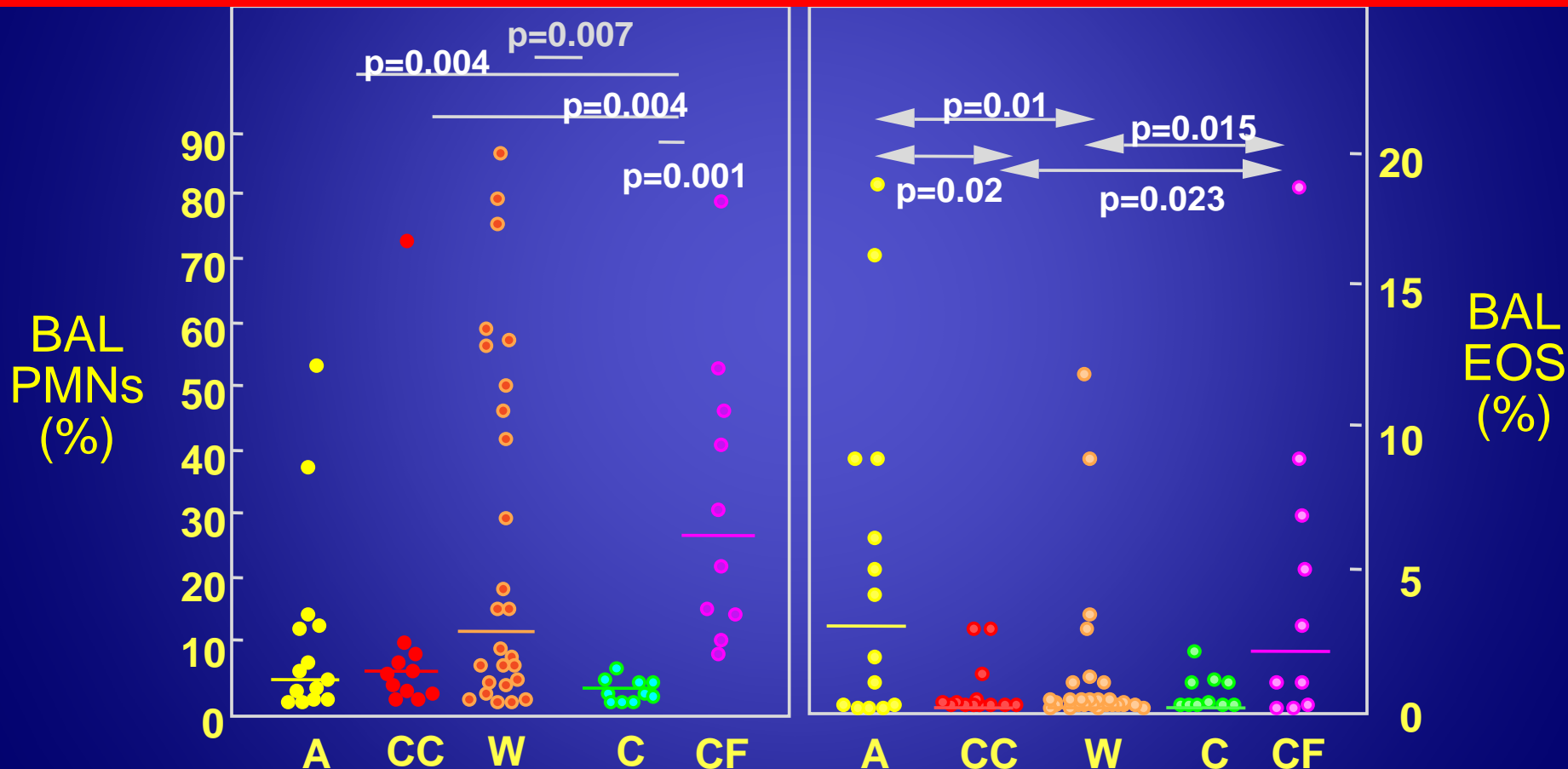
- *In utero* exposure to cigarette smoke increases BHR¹
- **Conclusion:** Mothers should avoid known allergens and tobacco smoke during pregnancy



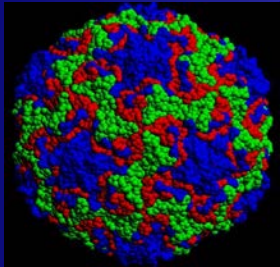
BAL Cells in Wheezing Children (WC) Compared to Normal Controls (NC)



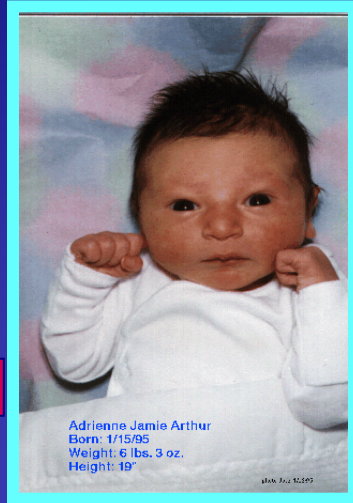
Childhood Asthma is Characterized by AW Eosinophilia while Infantile Wheezing Characterized by AW Neutrophilia



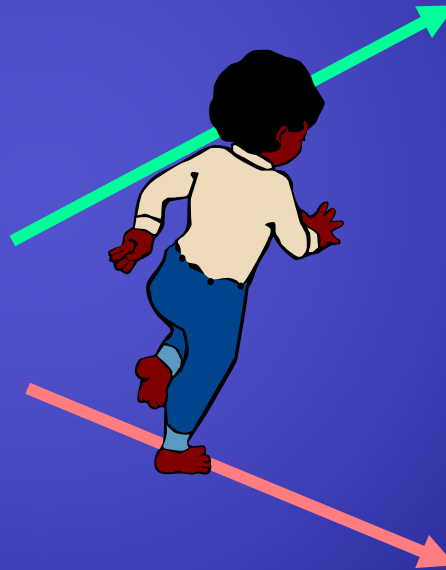
The Role of Infection



Viruses



**Wheezing
Illnesses**



**Resolution
or
Transient
Wheezing**

**Persistent
Wheezing
or
ASTHMA**

Asthma Risk Factors: Respiratory Illness

Healthy Infant

RSV
PIV
RV¹
MPV²
Chlamydia^{3,4}



Wheezing Illness

Resolution

Atopy

Asthma

RV⁴
MPV²
Mycoplasma⁵



Acute Exacerbation

¹Lemanske RF et al. J Allergy Clin Immunol 2005; 116(3):571-7.

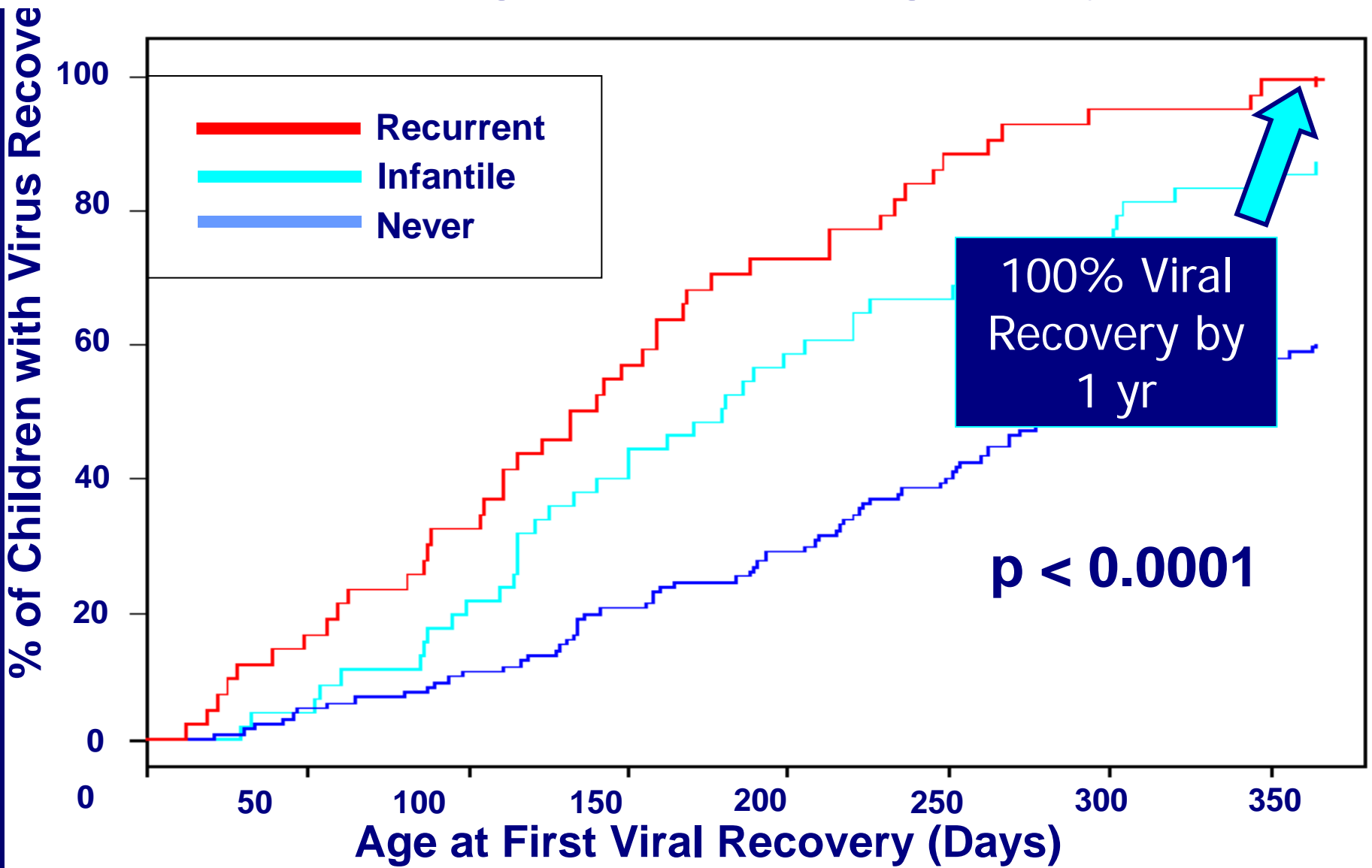
²Foulongne V et al. Pediatr Infect Dis J 2006; 25(4):354-9.

³Schmidt SM et al. Pediatr Allergy Immunol 2001; 12(5):257-65.

⁴Heymann PW et al. Pediatr Infect Dis J 2005; 24(11):S217.

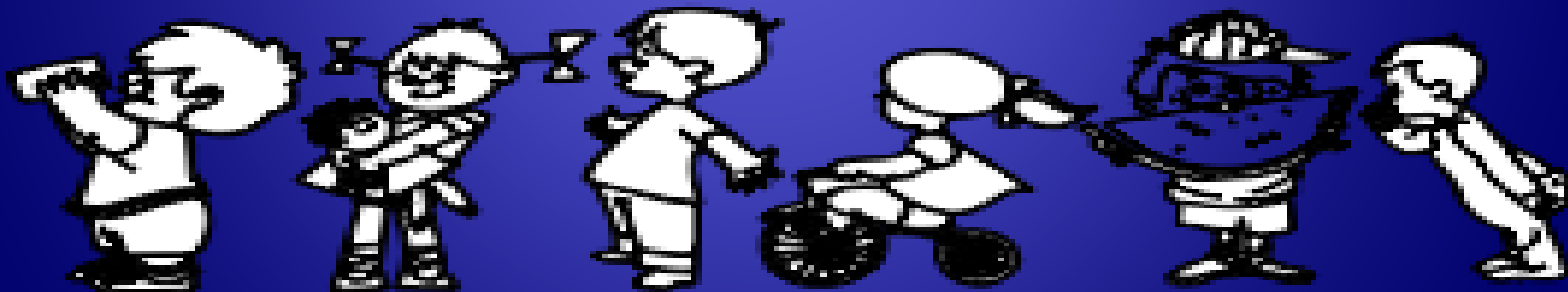
⁵Biscardi S et al. Clin Infect Dis 2004; 38(10):1341.

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



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!!!!!!

