

***Detection of Asthma in Infants,  
Toddlers, & Preschool Aged Children:  
Clinical Characteristics of Wheezers  
from Birth to Age 5 Years***

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## **Disclosure of Conflict of Interest Information**

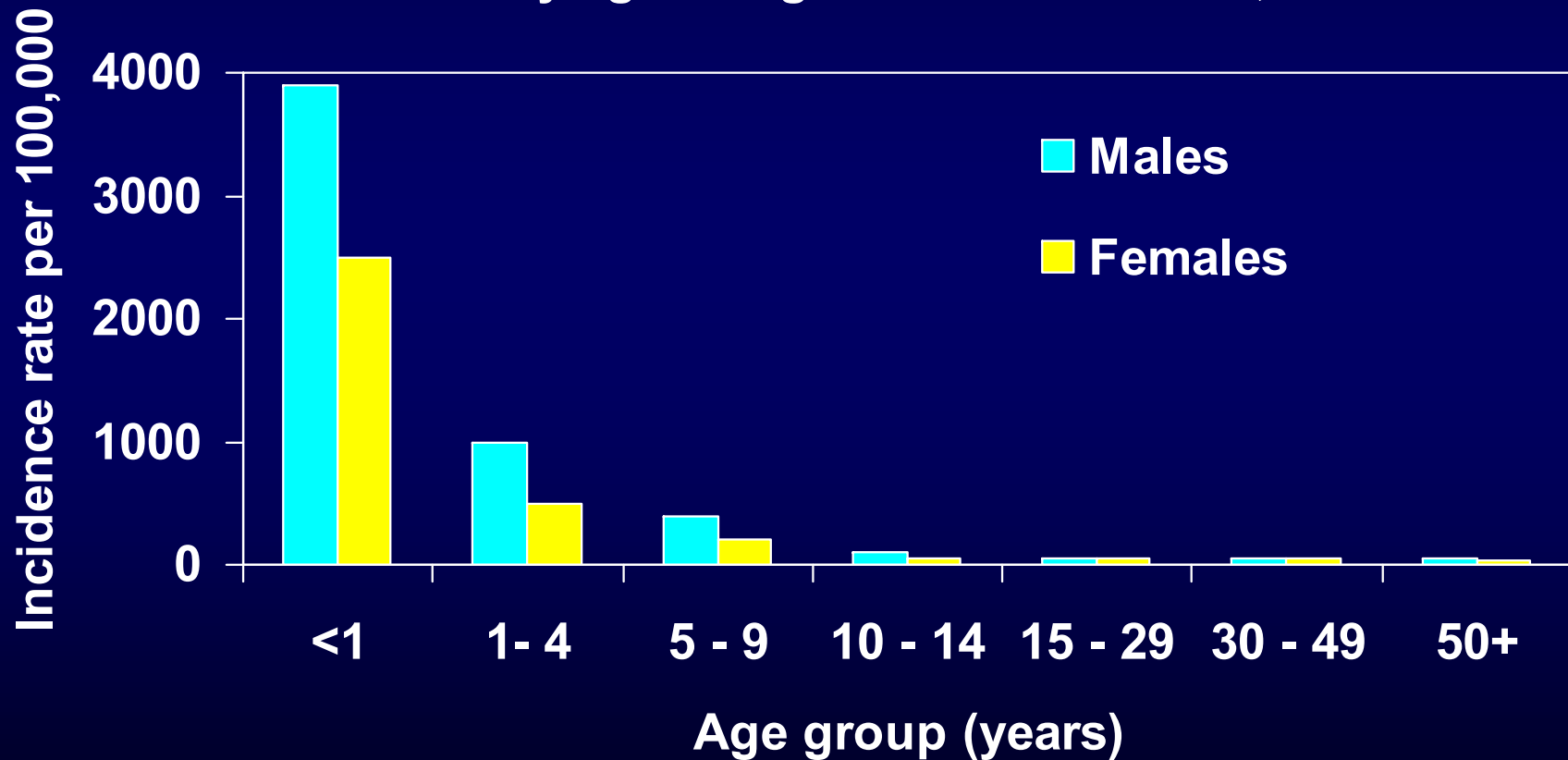
**I have the following relationship that exists related to this presentation:**

- Consultant/Advisory Board: AstraZeneca, Merck, GlaxoSmithKline, Genentech, Novartis, Aerocrine.
- Grant Monies: NHLBI
- Honoraria (Speaker): AstraZeneca, Merck, Novartis, GlaxoSmithKline, Aerocrine
- Other Fiduciary Positions: Chairperson of Workshops for the Annual Meeting of the Academy of Allergy, Asthma and Immunology.

# 80% of Asthma Begins in the First 5 Years of Life

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Asthma incidence by age and gender in Rochester, MN 1964-1983



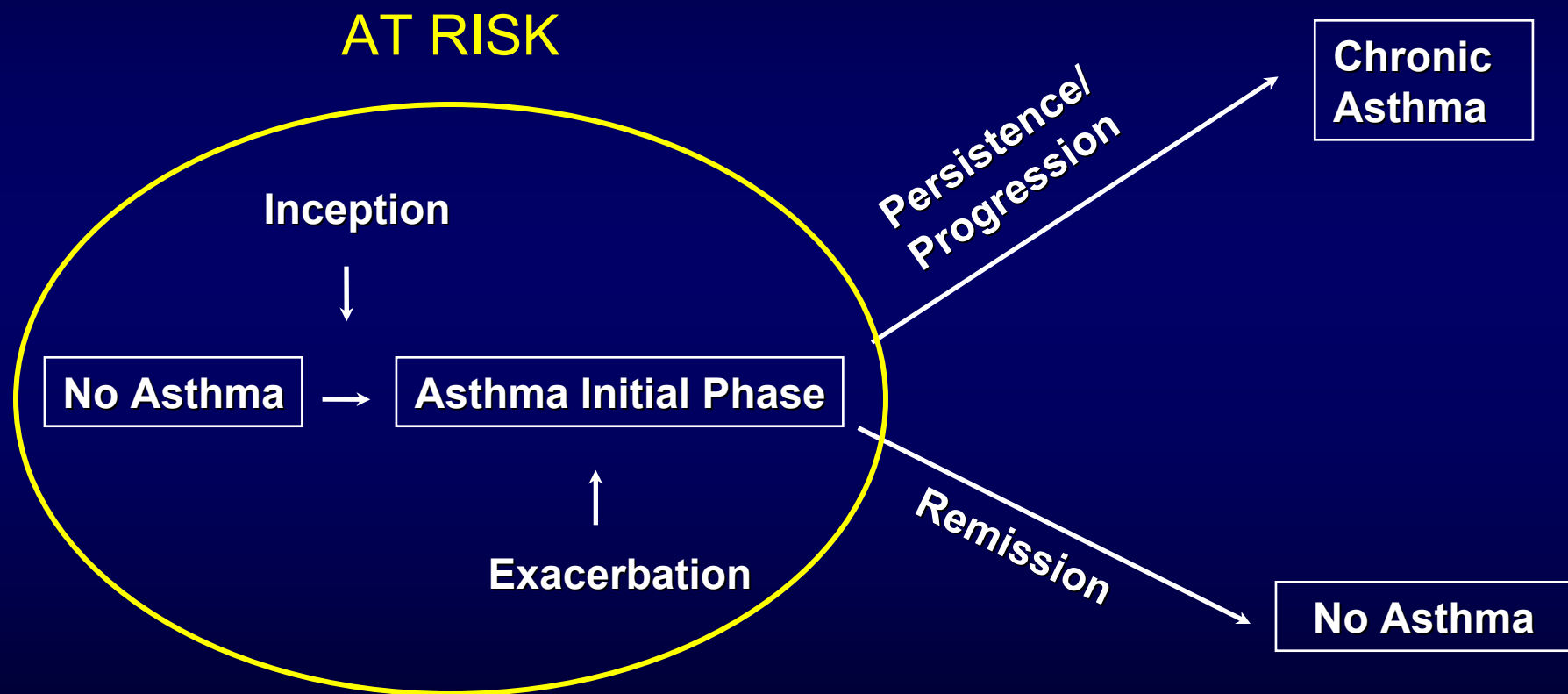
# *Asthma in Young Children – What's Different?*

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- Diagnosis is difficult
  - Lack of objective measurements
  - Lack of subjective awareness of symptoms
- Underdiagnosis is frequent
  - Wheezy bronchitis
  - Recurrent pneumonia
  - Recurrent croup
  - Chronic bronchitis
  - Recurrent upper respiratory infections

# Hypothetical Representation of the Natural History of Asthma

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# Wheezing Infants: When Is It Asthma?

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- Patterns of wheezing in infants:
  - Those who develop asthma
  - Those who do not develop asthma

# Phenotype

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“A set of characteristics that can be used to classify organisms into discrete groups”

# Asthma Phenotypes

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## CLINICAL FEATURES

- Age of onset
- Triggers
  - Allergen
  - Infection
  - Exercise
- Atopic vs non-atopic
- Natural history
- Severity
- Response to therapy

## PATHOPHYSIOLOGY

- Pattern of inflammation
  - Eosinophilic
  - Neutrophilic
- Biomarkers
  - eNO, EBC, ULTE4
- Lung function
  - Normal vs abnormal
  - Reversible vs fixed obstruction (BD, steroids)
  - AHR

# Phenotyping Childhood Asthma

- The process has just begun,
- We have a long way to go.
- But PRACTALL starts the process of explicitly distinguishing pediatric asthma phenotypes.

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## Review article

### Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report

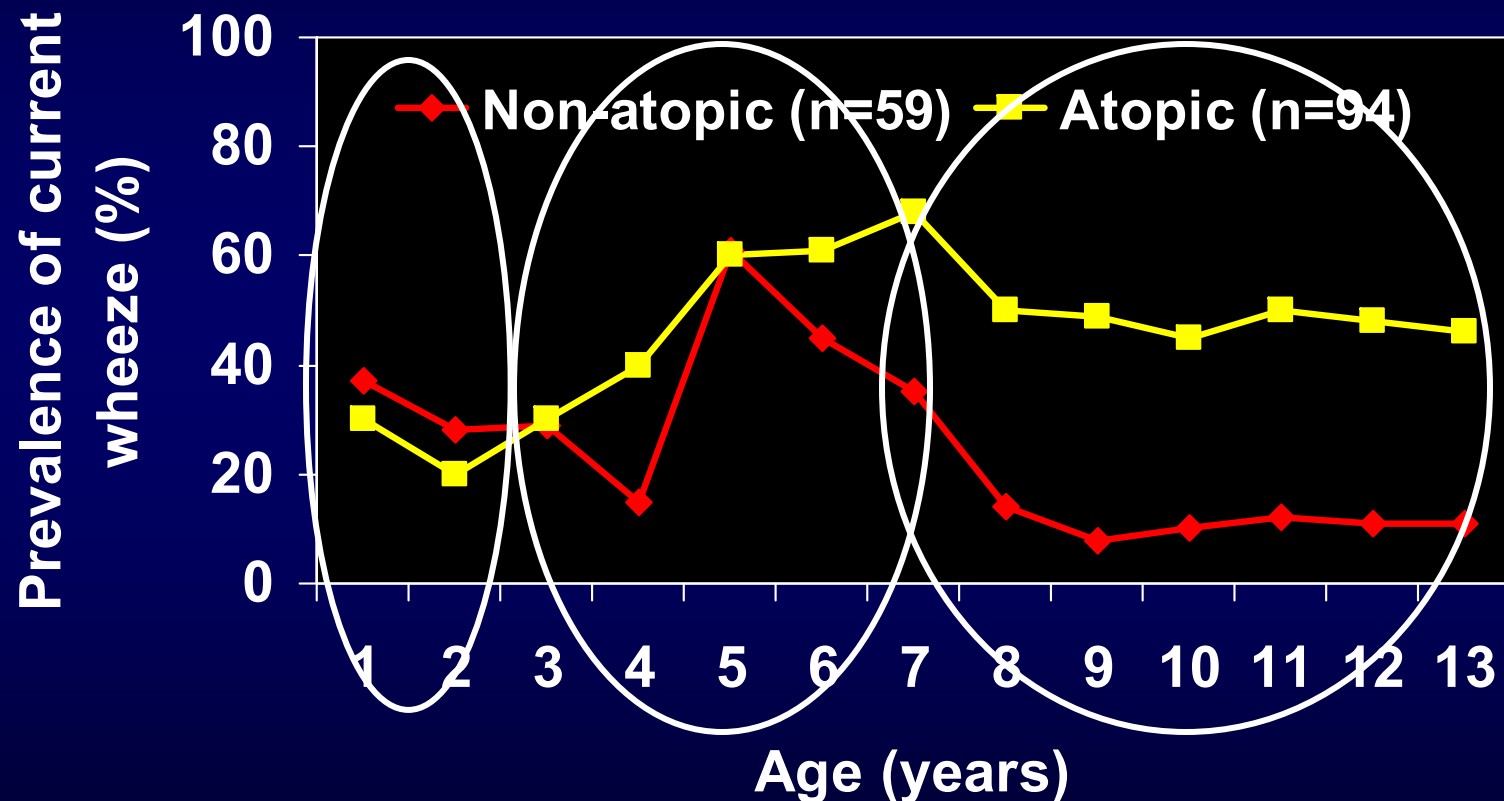
Asthma is the leading chronic disease among children in most industrialized countries. However, the evidence base on specific aspects of pediatric asthma, including therapeutic strategies, is limited and no recent international guidelines have focused exclusively on pediatric asthma. As a result, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology nominated expert teams to find a consensus to serve as a guideline for clinical practice in Europe as well as in North America. This consensus report recommends strategies that include pharmacological treatment, allergen and trigger avoidance and asthma education. The report is part of the PRACTALL initiative\*\*, which is endorsed by both academies.

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# German Multicentre Allergy Study

- Birth cohort from 1990 (n=1314)



By age 13 yrs, 90% of non-atopic wheezers had remission of symptoms, compared with 56% of atopic wheezers (p=0.0002)

# First issue in Phenotyping: Age

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- INFANTS (< 2 years)
- PRESCHOOL (2-5 years)
- SCHOOL AGE (6-12 years)
- ADOLESCENTS

**Phenotyping #2:**  
Intermittent vs. Persistent  
nature of symptoms.

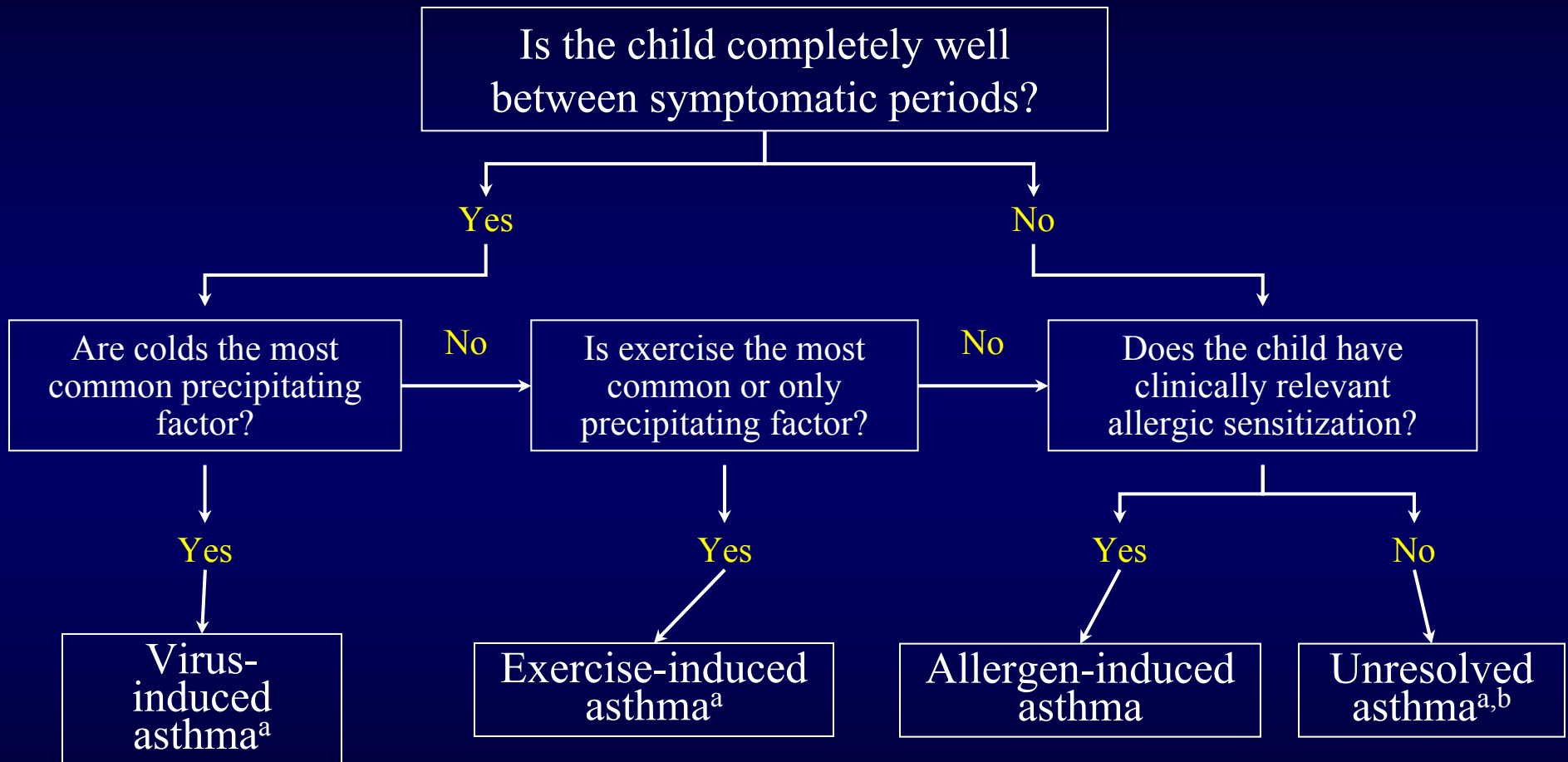
“Persistent” meaning chronically present, essentially every day  
in this case.

# Phenotyping #3 —subgrouping into common asthma childhood phenotypes

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- Virus-induced Asthma
- Exercise-induced Asthma
- Allergen-induced Asthma
- Non-allergic/Unresolved Asthma
  - Includes multiple possibilities
    - Stress, pollutants, tobacco/ irritants, unidentified allergens
- The phenotypes often overlap
- Confounding additional disorders are common

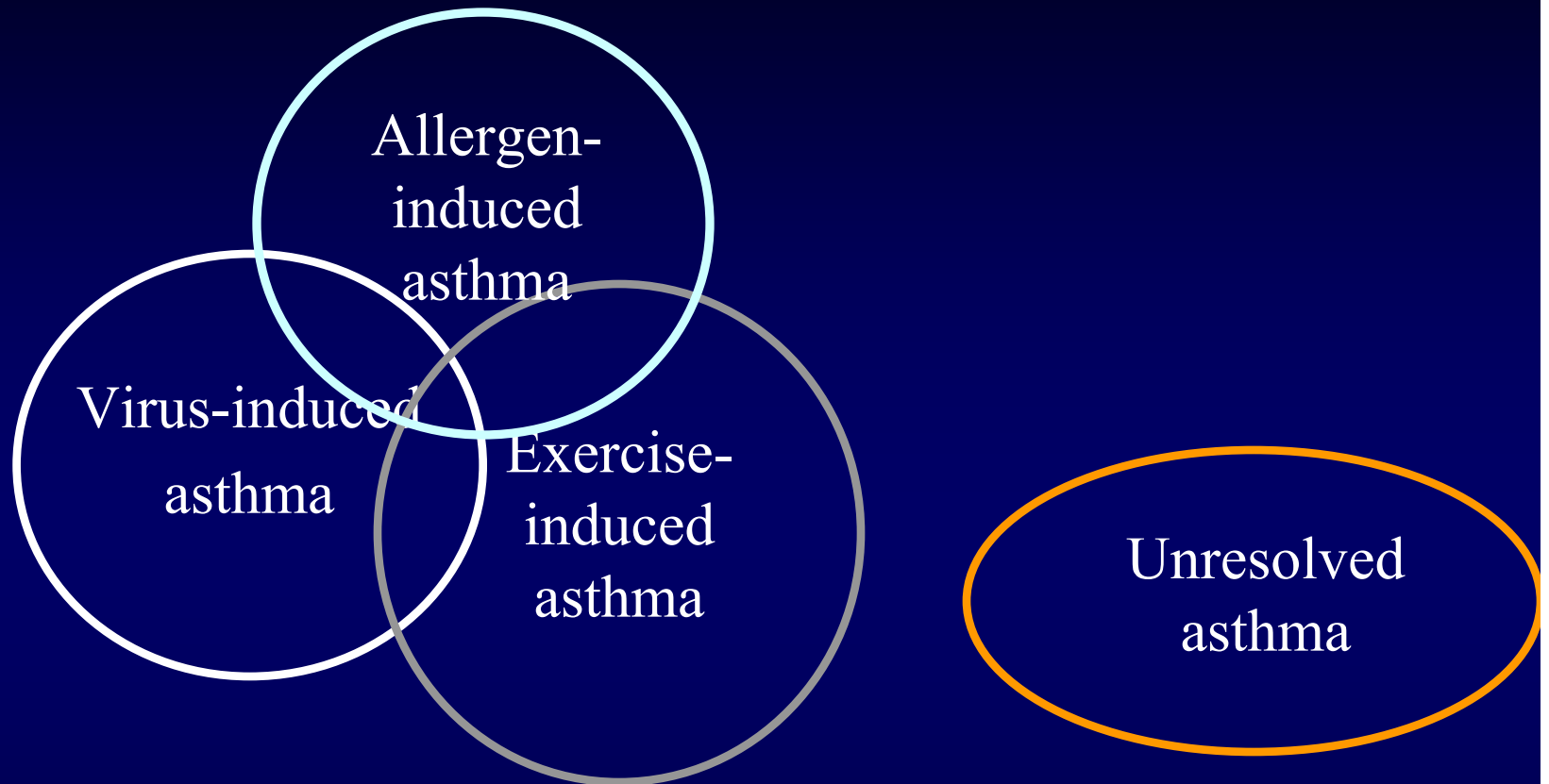
# Asthma Phenotypes in Children >2 Years of Age



<sup>a</sup>Children may also be atopic.

<sup>b</sup>Different etiologies, including irritant exposure and as-yet not evident allergies, may be included here.

# Asthma Phenotypes in Children >2 Years of Age



Virus-induced asthma<sup>a</sup>

Exercise-induced asthma<sup>a</sup>

Allergen-induced asthma

Unresolved asthma<sup>a,b</sup>

<sup>a</sup>Children may also be atopic.

<sup>b</sup>Different etiologies, including irritant exposure and as-yet not evident allergies, may be included here.

# Phenotyping #4: Severity

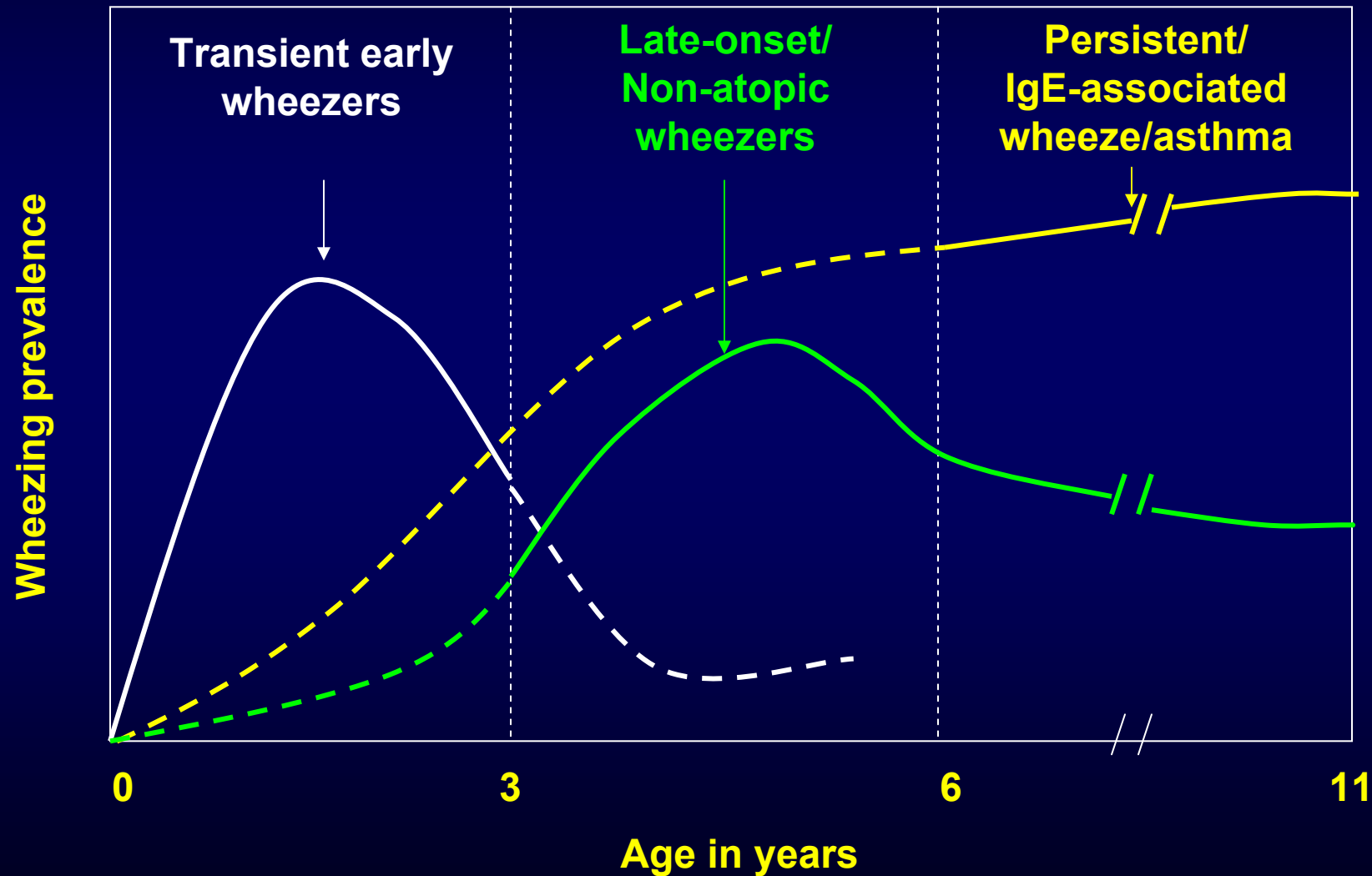
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- PRACTALL suggests a common sense approach to this.
  - “Severe” if it is severe
  - “Mild-Moderate” if it isn’t severe.
  - Recognize that severity can change from week to week in children.
  
- “Persistent and Unresponsive to Therapy” is a potentially different process than other forms of asthma, and can be considered a severity class
  - Reconsider differential diagnosis and confounders
  - Failure of medication compliance?

# Phenotypes of Early Childhood Wheezing

Pattern of Wheeze During 1 <sup>st</sup> 6 Years	0-3 Years	4-6 Years	% of Cohort
Never Wheeze			51%
Transient Early Wheeze			20%
Late-Onset Wheeze			15%
Persistent Wheeze			14%

# Different Wheezing Phenotypes in Early Childhood

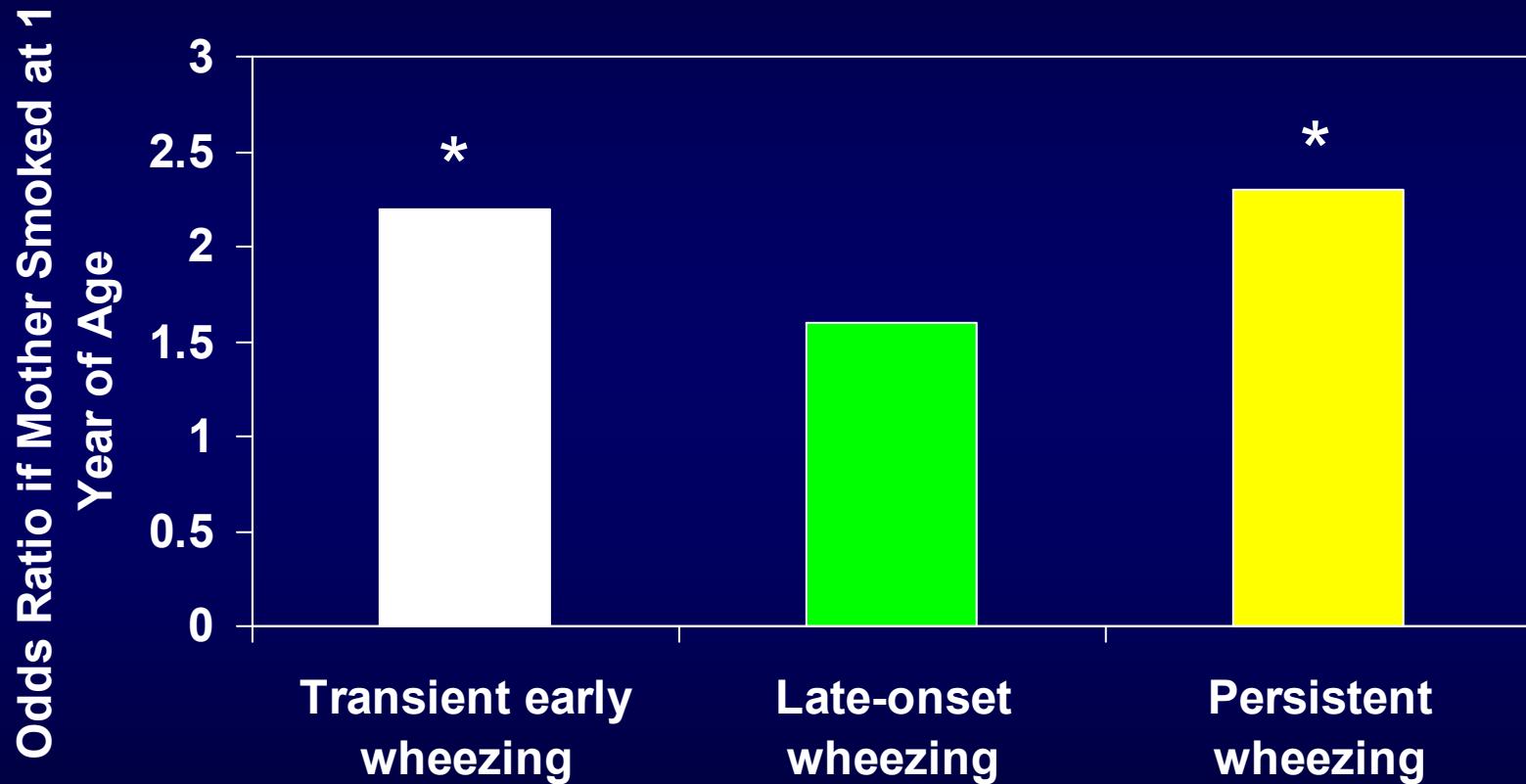


# Serum IgE Levels and Positive Skin Tests at 6 Years of Age

Category	Serum IgE (IU/ml)	Positive Skin Test (%)
No wheezing	28.1	34
Transient early wheezing	31.2	38
Late-onset wheezing	42.1	56
Persistent wheezing	65.6	51
	P=0.002	P<0.001

# Effect of Maternal Smoking on Wheezing

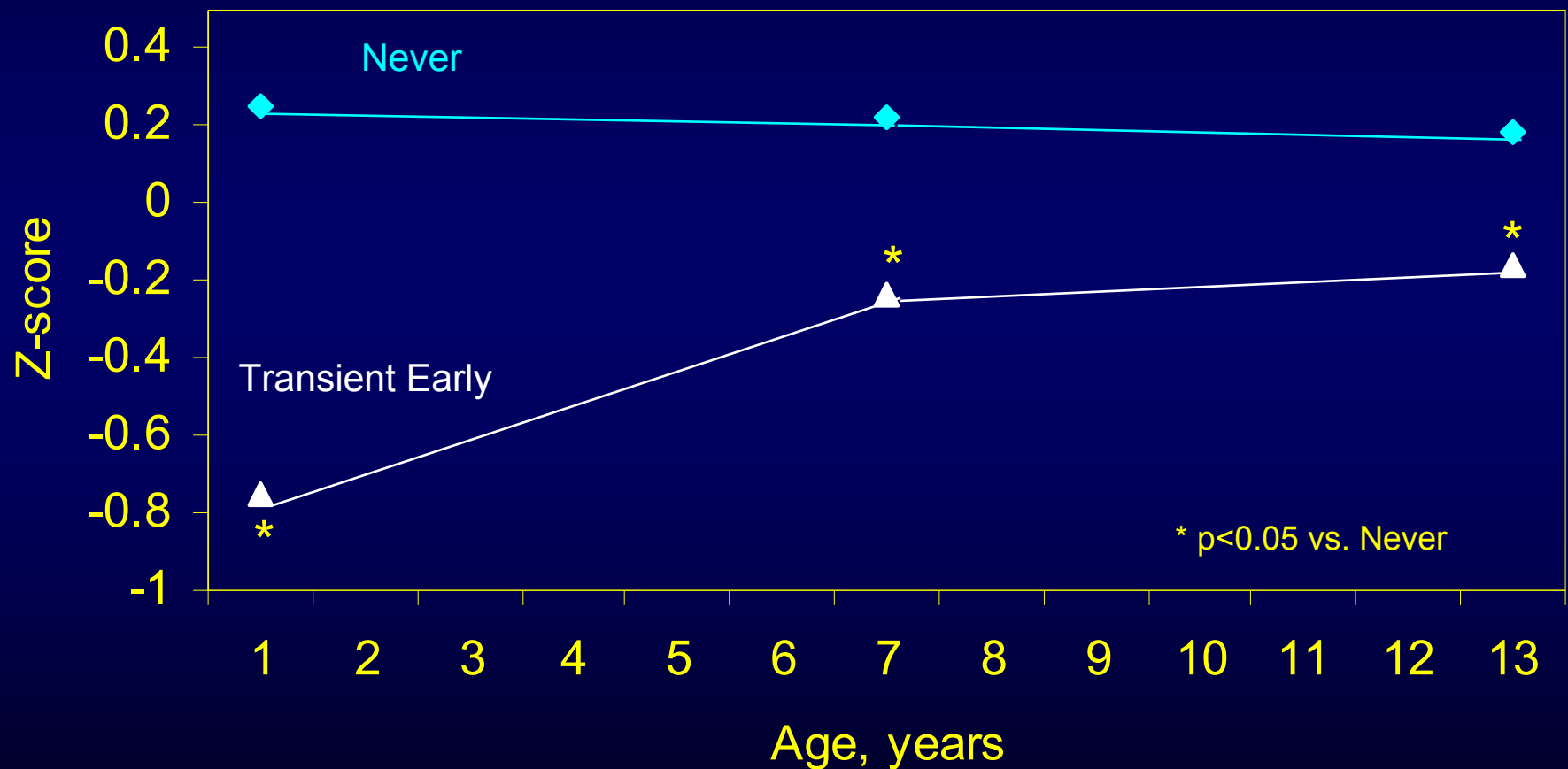
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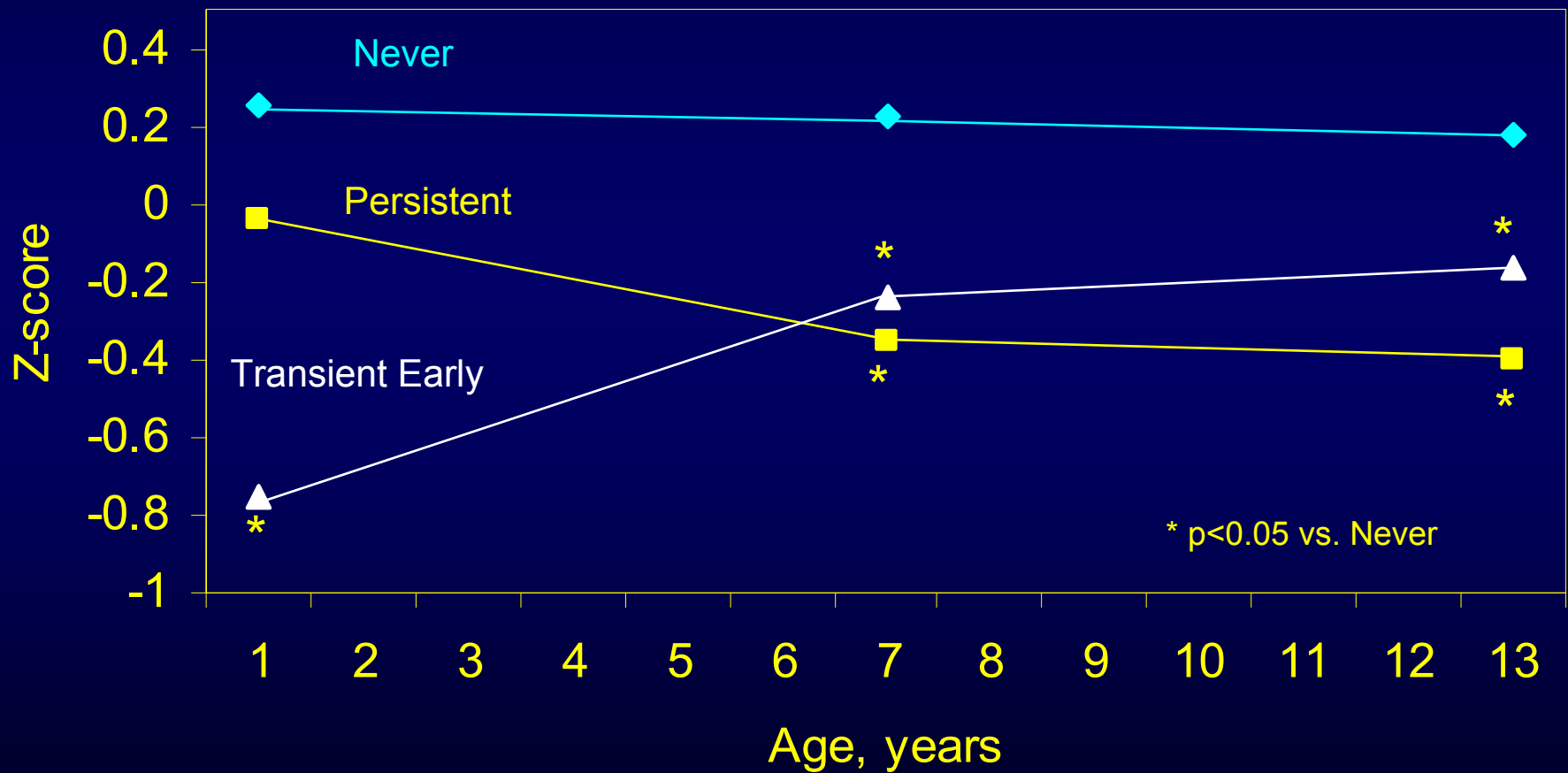
\*  $p < 0.01$

# Transient Early Wheezers Gain Lung Function Over Time

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# Persistent Wheezers Lose Lung Function Over Time



# Transient vs. Persistent Wheezers

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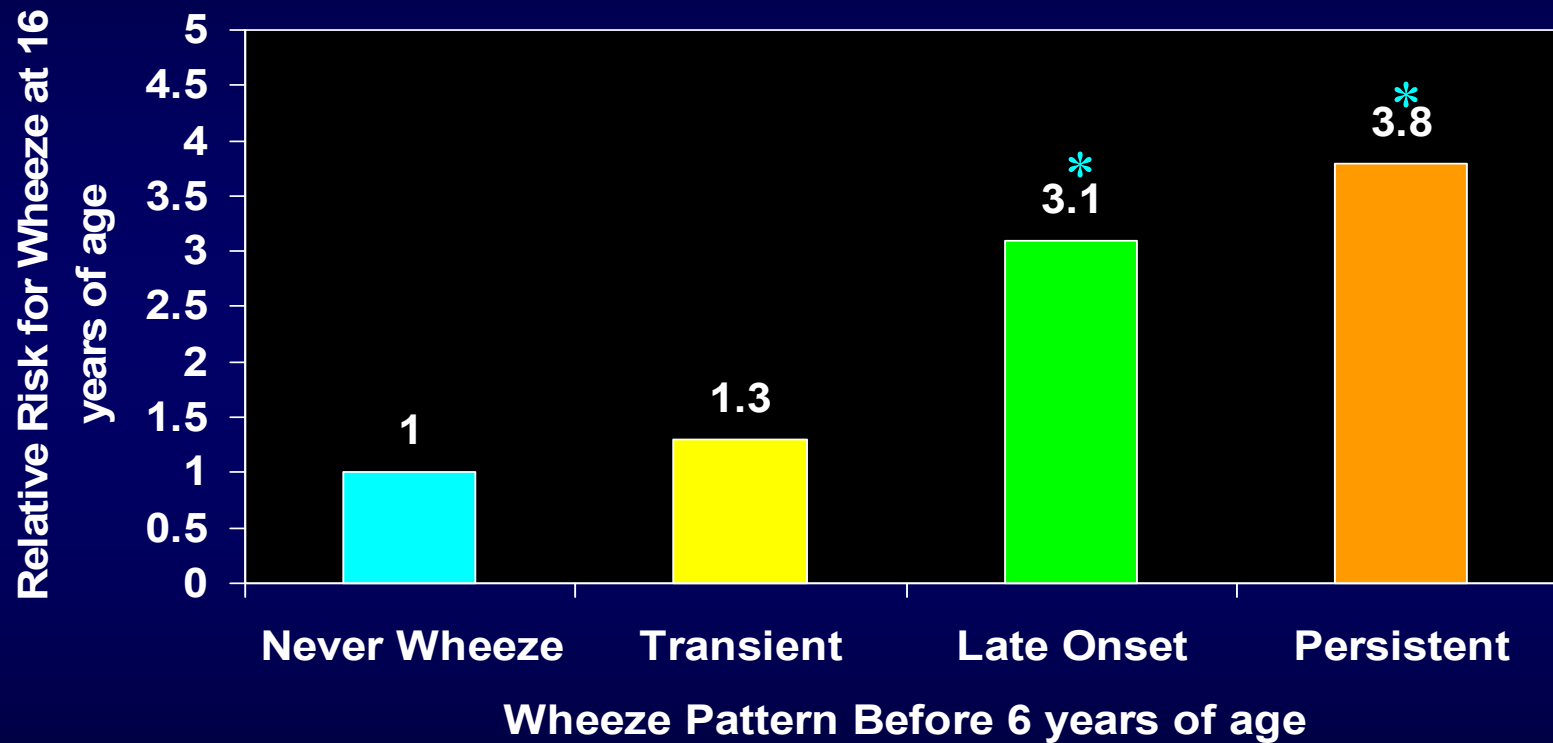
## Transient Wheezers

- Diminished lung function at birth, at 6 & 13 yrs of age
- Mother who smoked
- Mothers without asthma
- Normal IgE levels
- Negative skin tests

## Persistent Wheezers

- Normal lung function at birth but diminished at 6 & 13 yrs of age
- Mothers with asthma
- Elevated IgE levels at 9 months and 6 yrs
- Positive skin tests at 6 yrs of age

# Early Life Wheezing Phenotypes Correlate with Wheezing at 16 Years



\*  $p < 0.001$  compared with never wheezers

# Asthma Predictive Index

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- Identify high risk children (ages 2 & 3):
  - $\geq 4$  wheezing episodes in the past year (at least one must be MD diagnosed)

## One major criterion

OR

## Two minor criteria

- Parent with MD asthma
- MD atopic dermatitis
- Aeroallergen sensitivity

- Food sensitivity
- Peripheral eosinophilia ( $\geq 4\%$ )
- Wheezing not related to infection

# Asthma Predictive Index

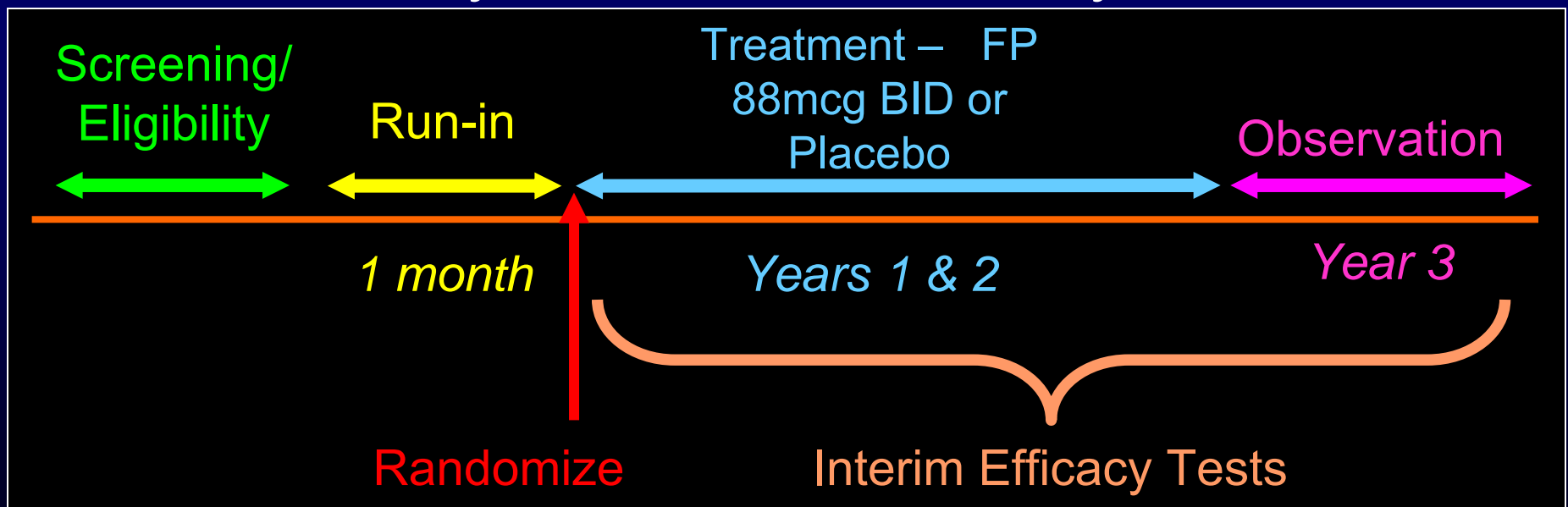
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Active Asthma	OR (95% CI)	Positive Predictive Value (%)	Negative Predictive Value (%)
At Yr 6	9.8 (5.6-17.2)	47.5%	91.6%
At Yr 13	5.7 (2.8-11.6)	51.5%	84.2%

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# The PEAK Trial

- Randomized, multicenter, double-blind, parallel group, placebo-controlled trial
- 285 children 24-47 months of age
- Positive asthma predictive index
- < 4 months of inhaled corticosteroid and < 4 courses of systemic steroid in last year



# PEAK: Allergen Sensitization

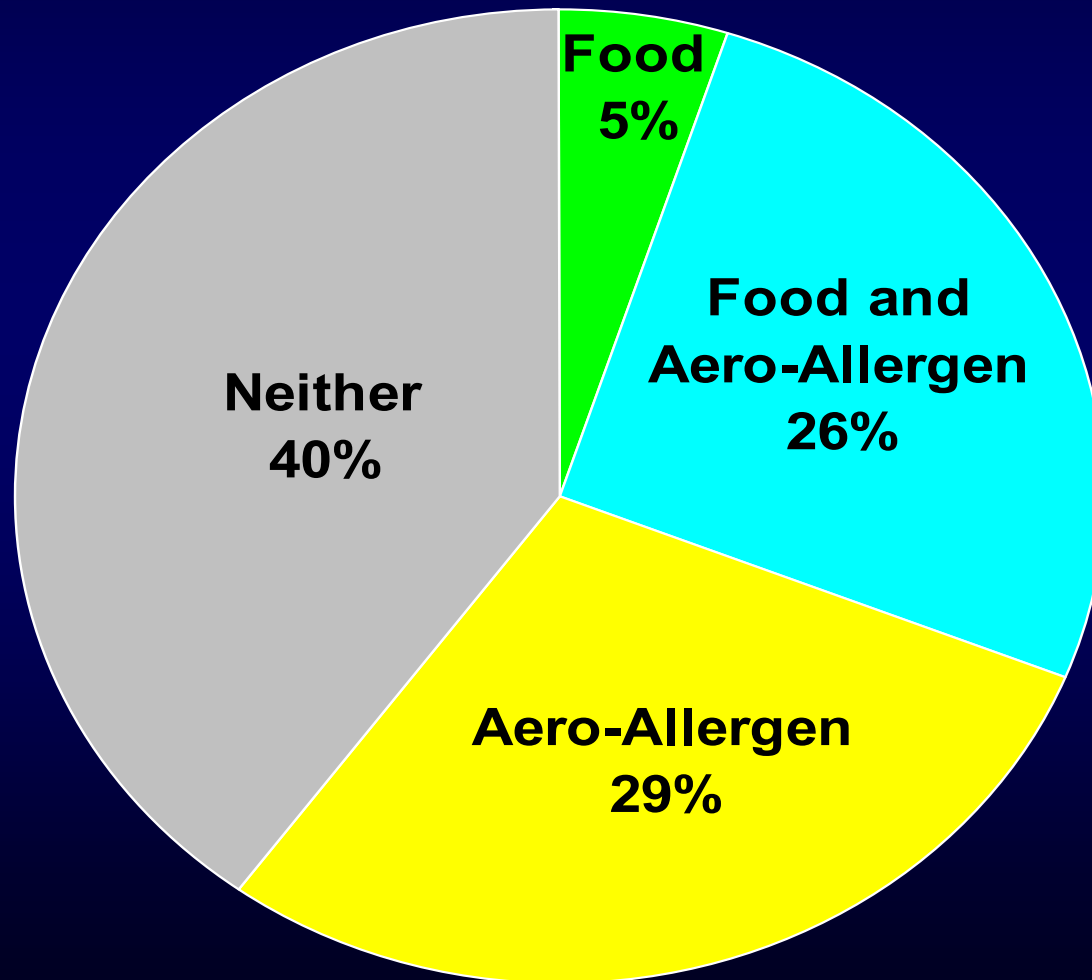
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- Multi-test II® skin prick test
- Food = egg, milk, peanut (3)
- Aero-Allergen = cat, dog, dust, grass, mold, roach, tree, weed (8)
  
- 90% of positive API due to either + FH or eczema
- 10% with skin test positivity alone excluded from this analysis



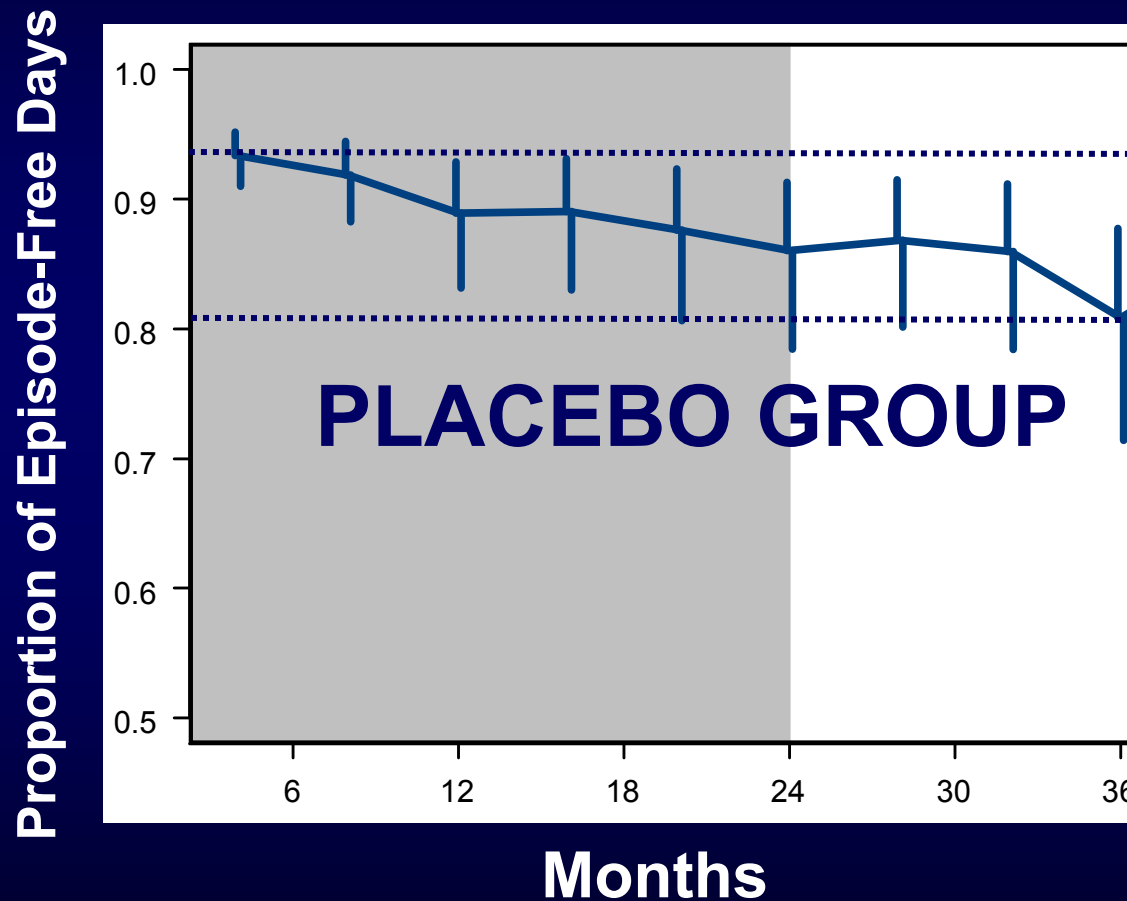
# Sensitization by Allergen Class

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- Skin test = 40%  
+ Skin test = 60%

# API Identifies Children at Risk for Persistence of Symptoms



# Predictors of Persistence of Asthma

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- 150 children at risk for asthma due to maternal asthma identified prenatally and followed until 6-8 yrs of age
- 28% developed asthma by 6-8 yrs
- Factors associated with asthma by 6-8yrs
  - Higher IgE level at 6 months (OR 2.15)
  - Parenting difficulties at 3 weeks of age (OR 2.07)

# Does Airway Responsiveness in Infancy Predict Persistence of Asthma?

- 253 white infants in Western Australia randomly recruited before birth
- 120 were followed until 6 years of age
- At age 6, 21.7% had current MD-diagnosed asthma
- Increased airway responsiveness to histamine at 1 month of age (prior to LRTI) was significantly associated with:
  - MD-diagnosed asthma
  - Decreased FEV<sub>1</sub> and FVC

At age 6 years  
P<0.0001

# Does Airway Responsiveness in Infancy Predict Persistence of Asthma?

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- 129 infants recruited from Pulmonary Clinic (11-17 months of age) with  $\geq 3$  episodes of wheezing followed for 4 years
- 20% continued to wheeze at 4 years
- Compared to those who became asymptomatic, persistent wheezers had:
  - Lower  $V_{\max}$ FRC at initial evaluation
  - Similar measures of airway responsiveness at initial evaluation, but had greater airway responsiveness at 30 months of age
    - However, no cut-off point for AHR that determined subsequent clinical progression could be identified

# Allergen-Specific IgE and Asthma at School-age

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- 82 children hospitalized for wheezing at <2 yrs of age
- Allergen specific IgE levels to foods & inhalants on samples from enrollment
- Asthma at school age if (1) use of continuous asthma meds, or (2) repeated or prolonged wheezing episodes in past year and positive exercise challenge

# Allergen-Specific IgE and Asthma at School-age

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- 46% sensitized to foods, 18% sensitized to inhalants
- Specific IgE to egg white or wheat increased asthma risk
  - Egg white OR for asthma 2.85
  - Wheat OR for asthma 4.93
- Phadiatop Combi (egg white, cow milk, fish, wheat, peanut, soybean)
  - Level of 0.70 kU/L OR for asthma 2.97
  - Level of 3.5 kU/L OR for asthma 4.23
- Phadiatop Combi (timothy grass, birch, mugwort, cat, dog, horse, dust mite, *C herbarum*)
  - Level of  $\geq 0.35$  kU/L OR for asthma 9.75

# Wheezing Children – When is it Asthma?

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- Persistent asthma is more likely to develop in the context of:
  - Family history of asthma or atopy (especially maternal)
  - Personal history of atopy (atopic dermatitis/eczema, allergic rhinitis, food allergy)
  - Exposure to aeroallergens and non-specific airway irritants
    - House dust mite (especially exposure in 1<sup>st</sup> year of life)
    - Animals – although recent reports bring this into question
    - Tobacco smoke – both intrauterine exposure and postnatal exposure

# Diagnosing Asthma

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- Historical/Clinical: episodic symptoms of airflow obstruction
  - ❖ Wheezing, chest tightness, breathlessness, dyspnea, cough
- Symptoms worsen/provoked by exercise and/or cold air exposure
- Awakening at night due to respiratory symptoms (cough, tightness, wheeze)
- Response to appropriate pharmacologic agents – bronchodilators, corticosteroids
- Co-existing conditions – eczema, rhinitis, sinusitis, food allergy
- Pulmonary function testing: obstruction to airflow which is at least partially reversible by bronchodilators
- Differential diagnosis: exclusion of other diagnosis

# Dilemma of Asthma Diagnosis in Preschool Children

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- Health care professionals are encouraged to make a positive diagnosis of asthma whenever recurrent wheezing, breathlessness or cough occurs
- Diagnosis of “asthma” implies an underlying syndrome with airway inflammation and which has a specific protocol for management
- The younger the child, the more likely than an alternative diagnosis may explain the recurrent wheeze
- Lack of uniform pathogenesis of children with recurrent wheezing impact treatment approach and effectiveness

# Conclusions for the Evaluation of Asthma in Early Childhood

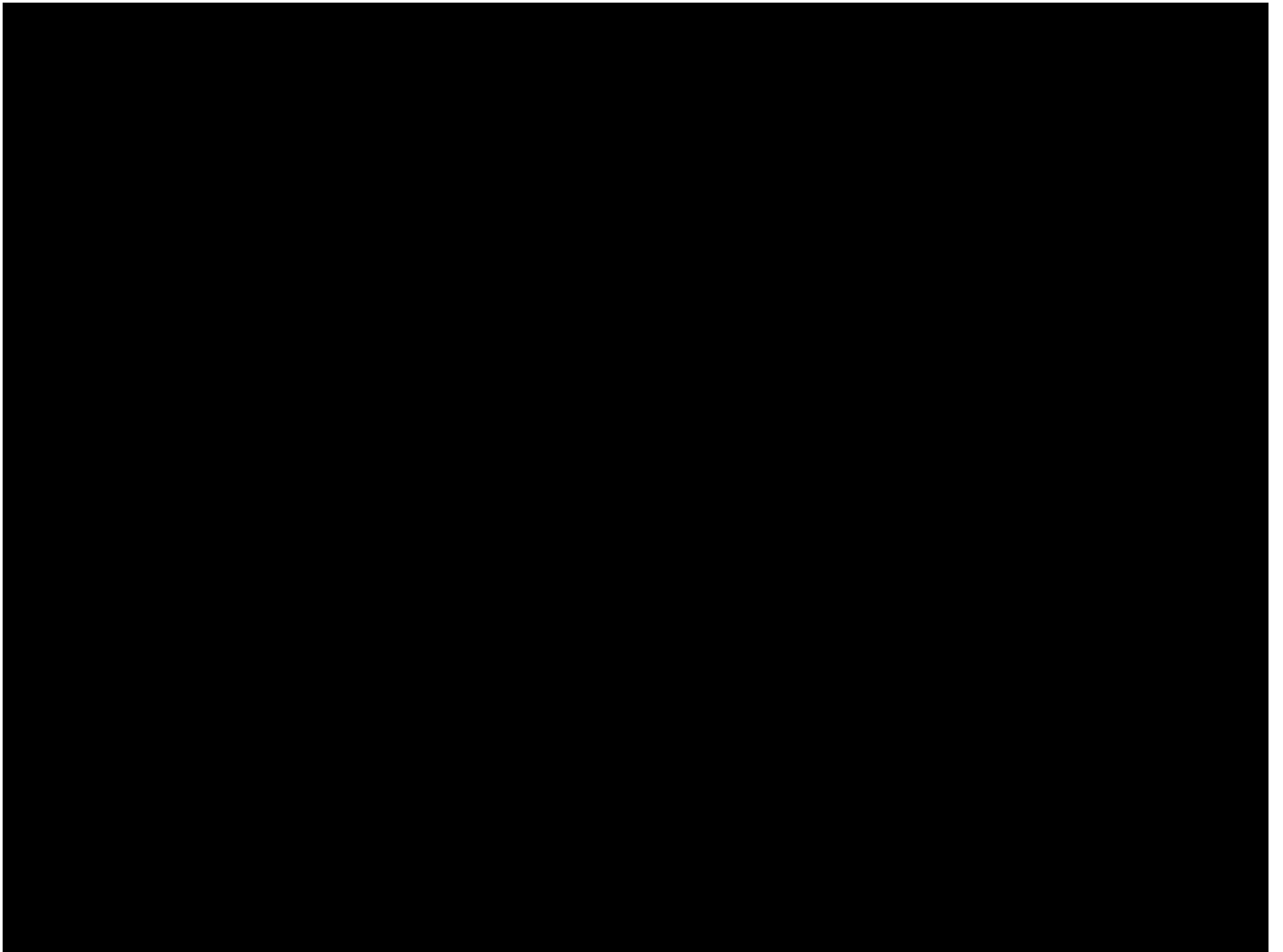
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- Most asthma has its inception in the preschool years
- Wheezing illness is common in the first three years of life
- Most children with wheezing have a benign outcome
- Some children with wheezing will have a chronic inflammatory disease of the lower airways with loss of lung function by age 6

# Conclusions for the Evaluation of Asthma in Early Childhood

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- Wheezing illness in early childhood should be evaluated in the context of relation to viral infection, parental history, past medical history, and allergic disposition
- Intervention strategies represent an opportunity for the secondary prevention of asthma



# ***Assessment and Management of Potential Risk and Impairment for Asthma in Infants, Toddlers, and Preschool Children***

**Leonard Bacharier, M.D.**

**Associate Professor of Pediatrics  
Clinical Director, Division of Allergy, Immunology, and  
Pulmonary Medicine**



# Definitions:

## Severity, Control, and Responsiveness

- Assessment and monitoring of asthma are closely linked to the concepts of severity, control, and responsiveness:
  - **SEVERITY**: the intrinsic intensity of the disease process; most easily and directly measured in a patient who is not currently receiving long-term control treatment
  - **CONTROL**: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met
  - **RESPONSIVENESS**: the ease with which control is achieved by therapy

## Classification of Asthma Severity (Children 0-4 years of age)

Components of Severity		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime Awakenings	0	1-2X/month	3-4X/month	>1X/week
	Short-acting beta2-agonist use for symptom control	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations (consider frequency and severity)	0-1/year	≥2 exacerbations in 6 months requiring oral steroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma (i.e. POSITIVE API)		
		Frequency and severity may fluctuate over time Exacerbations of any severity may occur in patients in any severity category			

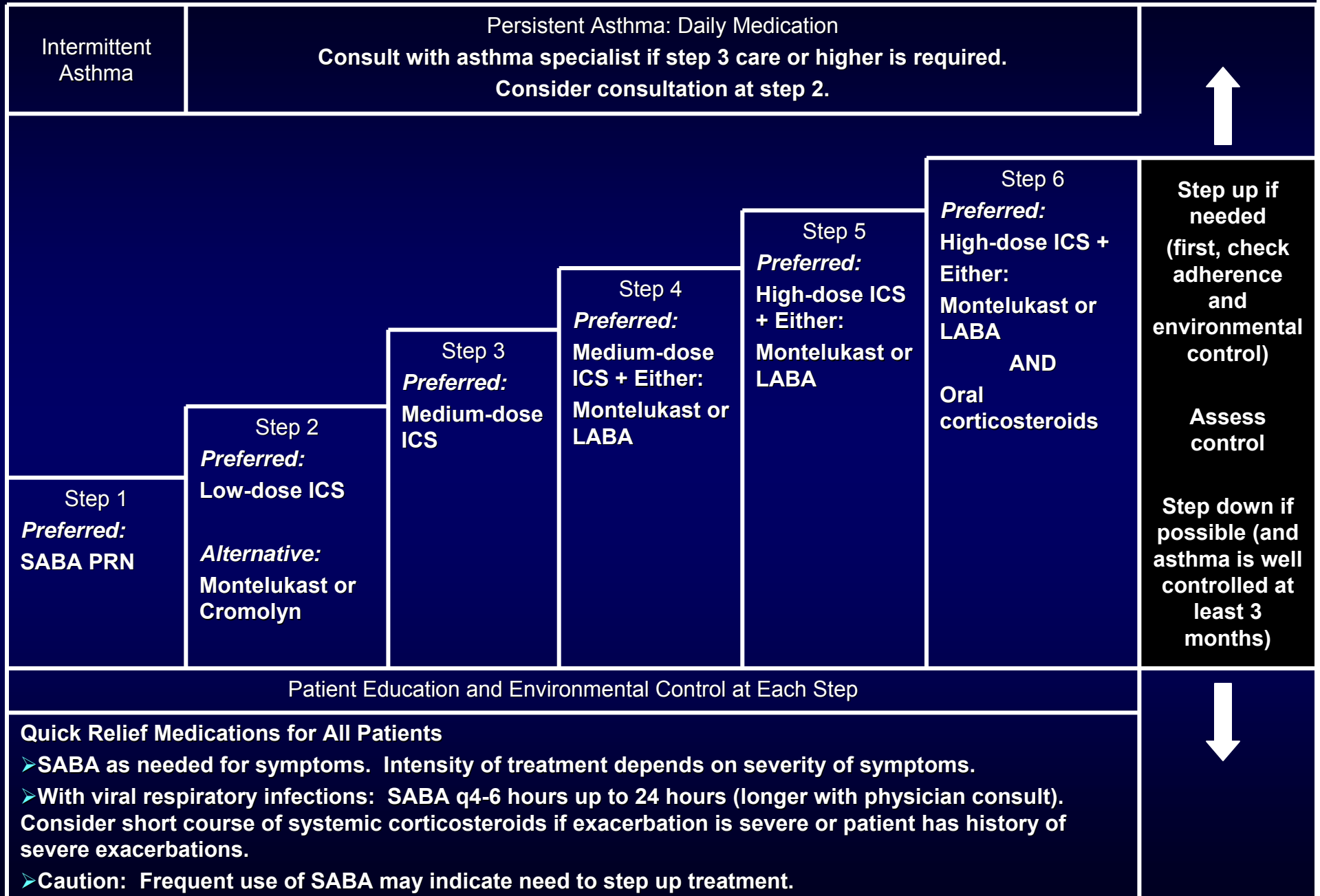
Components of Control		Classification of Asthma Control (Children 0-4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime Awakenings	1X/month	>1X/month	>1X/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta2-agonist use for symptom control	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year	2-3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		<p>Maintain current treatment</p> <p>Regular follow up every 1-6 months</p> <p>Consider step down if well controlled for at least 3 months</p>	<p>Step up (1 step) and Reevaluate in 2-6 weeks</p> <p>If no clear benefit in 4-6 weeks, consider alternative diagnoses or adjusting therapy</p> <p>For side effects, consider alternative treatment options</p>	<p>Consider short course of oral systemic corticosteroids</p> <p>Step up (1-2 steps), and Reevaluate in 2 weeks</p> <p>If no clear benefit in 4-6 weeks, consider alternative diagnoses or adjusting therapy</p> <p>For side effects, consider alternative treatment options</p>

# When to Initiate Daily Asthma Therapy for Infants and Young Children Under 5

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- $\geq 3$  episodes/year of wheezing lasting more than 1 day affecting sleep in a child with
  - atopic dermatitis and or parental asthma
  - or 2 of the following – physician diagnosis of allergic rhinitis, peripheral eosinophils, or wheezing apart from colds
- Symptomatic treatment more than 2 times a week
- $\geq 2$  severe exacerbations less than 6 weeks apart

# Stepwise Approach for Managing Asthma in Children 0-4 Years of Age



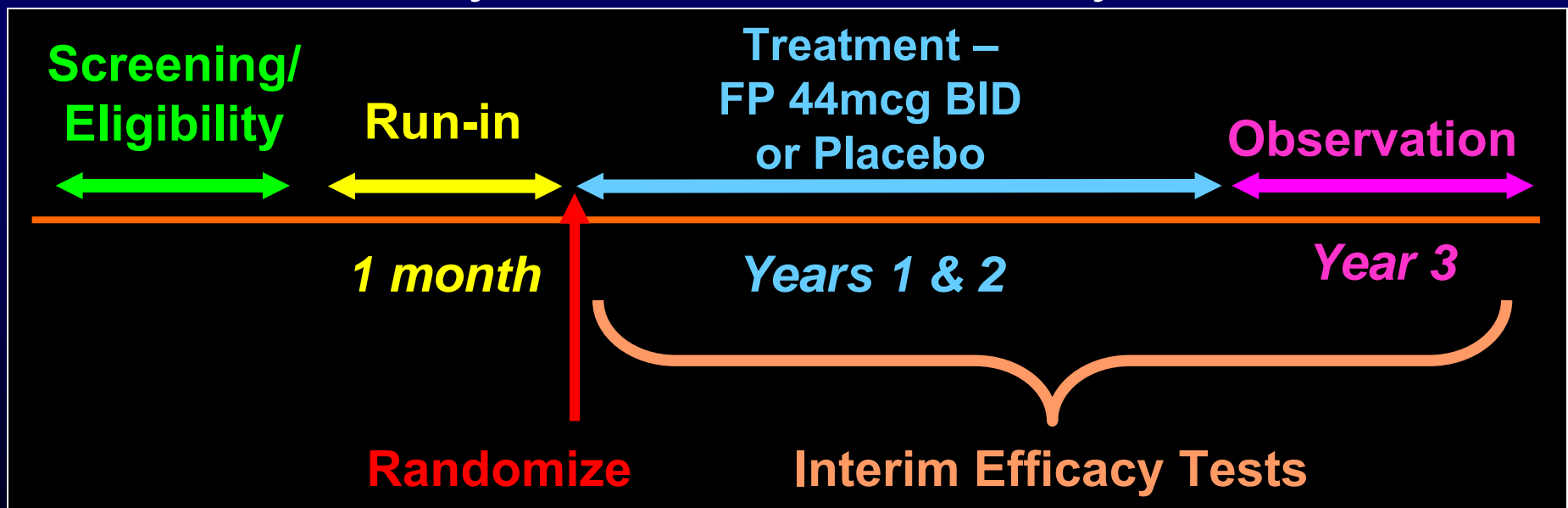
# Why Treat Preschool Children with Recurrent Wheezing?

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- Prevention of disease progression
- Minimization of ongoing or recurrent symptoms and/or exacerbations

# The PEAK Trial

- Randomized, multicenter, double-blind, parallel group, placebo-controlled trial
- 285 children 24-47 months of age
- Positive asthma predictive index
- < 4 months of inhaled corticosteroid and < 4 courses of systemic steroid in last year



# PEAK: Episode-free Days During Observation Year



# PEAK: Outcomes During Observation Year

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## ➤ No differences between groups:

- Time to additional controller medication
- Number of exacerbations requiring systemic corticosteroid bursts
- Unscheduled physician visits
- Hospitalizations
- Bronchodilator use
- Montelukast use
- Lung function (respiratory system reactance)



**Thus, initiation of ICS  
therapy in 2-3 year old  
children with positive  
APIs does not alter the  
course of preschool  
wheezing once therapy is  
discontinued**

# Secondary Prevention of Asthma by the Use of Inhaled Fluticasone Propionate in Wheezy Infants (IFWIN)

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- Prospective longitudinal cohort
- 200 children (<5 y/o) with parental atopy and 1 prolonged (>1 month) or 2 MD-confirmed wheezing episodes
- Randomized double-blind placebo-controlled trial
  - Fluticasone propionate 100 $\mu$ g BID, stepped down every 3 months to minimum required
  - Open label fluticasone added if symptoms persisted and stepped down to minimum required
- Followed for first 5 years of life
- Hypothesis: To prevent loss of lung function and worsening asthma later in childhood, anti-inflammatory treatment needs to be started early in life

# Secondary Prevention of Asthma by the Use of Inhaled Fluticasone Propionate in Wheezy Infants (IFWIN)

	Placebo n=88	Treatment n=85	Odds ratio (95% CI)	p
Current wheeze*	41 (47)	44 (52)	1.18 (0.63-2.21)	0.61
Further adjusted current wheeze†			1.23 (0.64-2.38)	0.53
Doctor diagnosis of asthma*	56 (64)	52 (61)	0.88 (0.46-1.66)	0.68
Further adjusted doctor diagnosis of asthma†			0.92 (0.48-1.76)	0.80
Current asthma medications*	58 (66)	56 (66)	1.00 (0.51-1.93)	0.99
Further adjusted current asthma medication†			1.07 (0.54-2.12)	0.85
Current asthma and asthma medication*	40 (45)	43 (51)	1.18 (0.63-2.22)	0.61
Further adjusted current asthma and asthma medication†			1.23 (0.64-2.37)	0.53

\*Adjusted for age of onset of wheeze, passive smoking, maternal asthma, pet exposure, sex and age at randomisation.  
†Additionally adjusted for addition of open label fluticasone propionate.

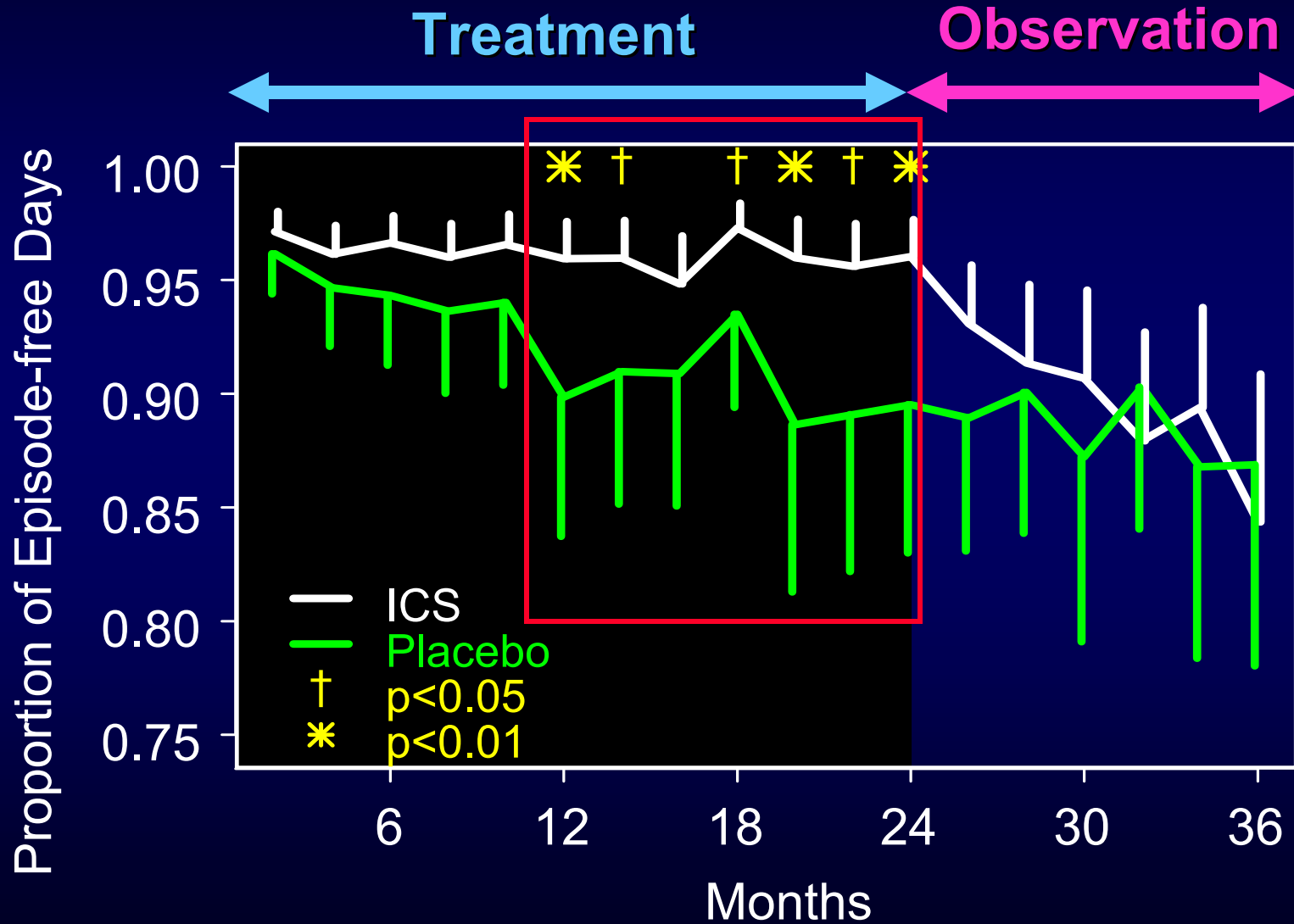
Table 2: Wheeze, asthma, and medication use at age 5 years in the treatment group compared with the placebo group

**In addition, no effect on pulmonary function**

**Inhaled Corticosteroids, When  
Given Continuously To Preschool  
Children With Parental  
Atopy/Asthma, Do Not Alter the  
Course of Early Childhood Asthma**

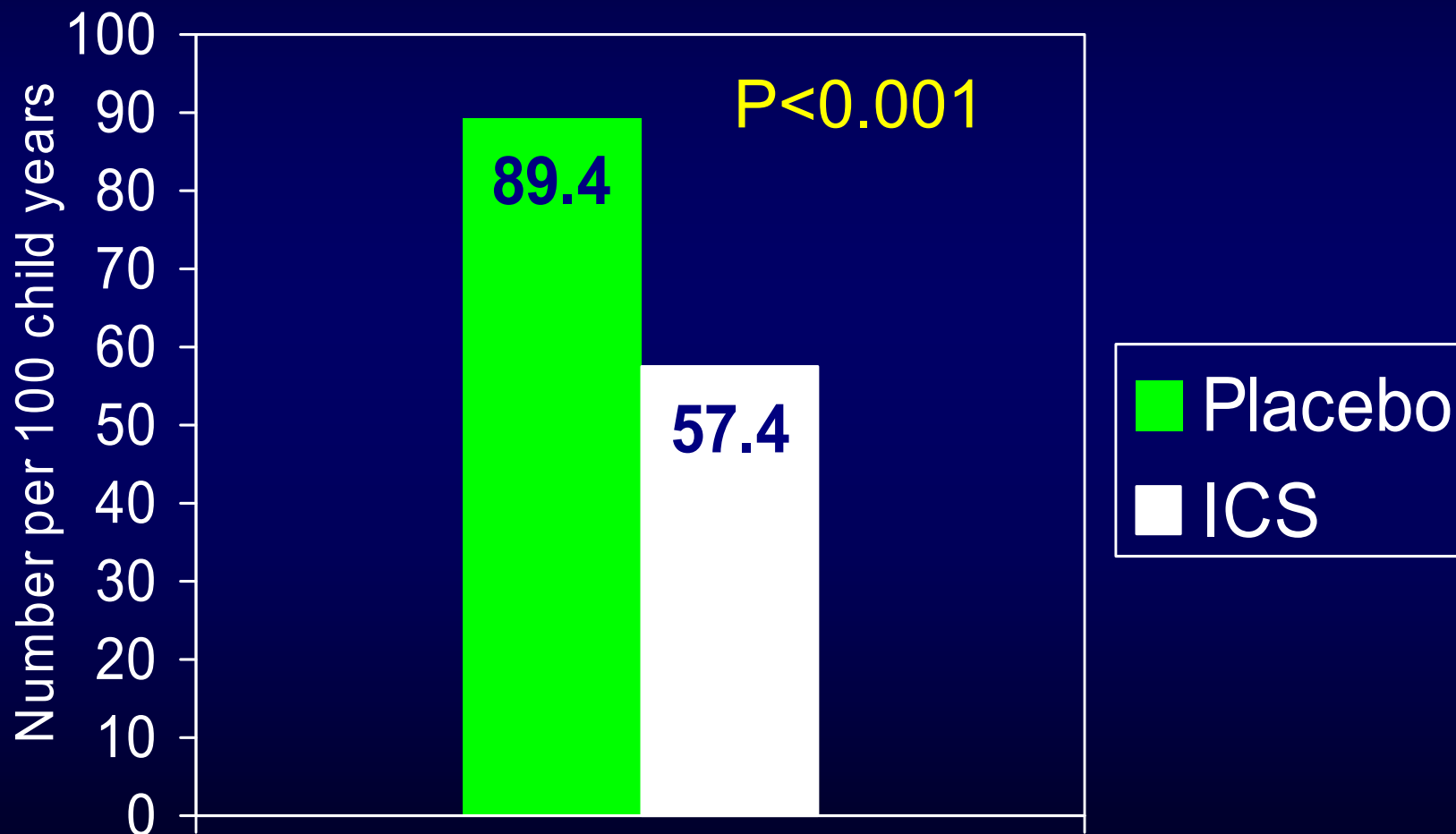
*But Do They Improve Symptom Control  
While They Are Being Used? And If So, At  
What Cost?*

# PEAK: Episode-free Days During the Entire Study



# PEAK: ICS Effect During Treatment Phase

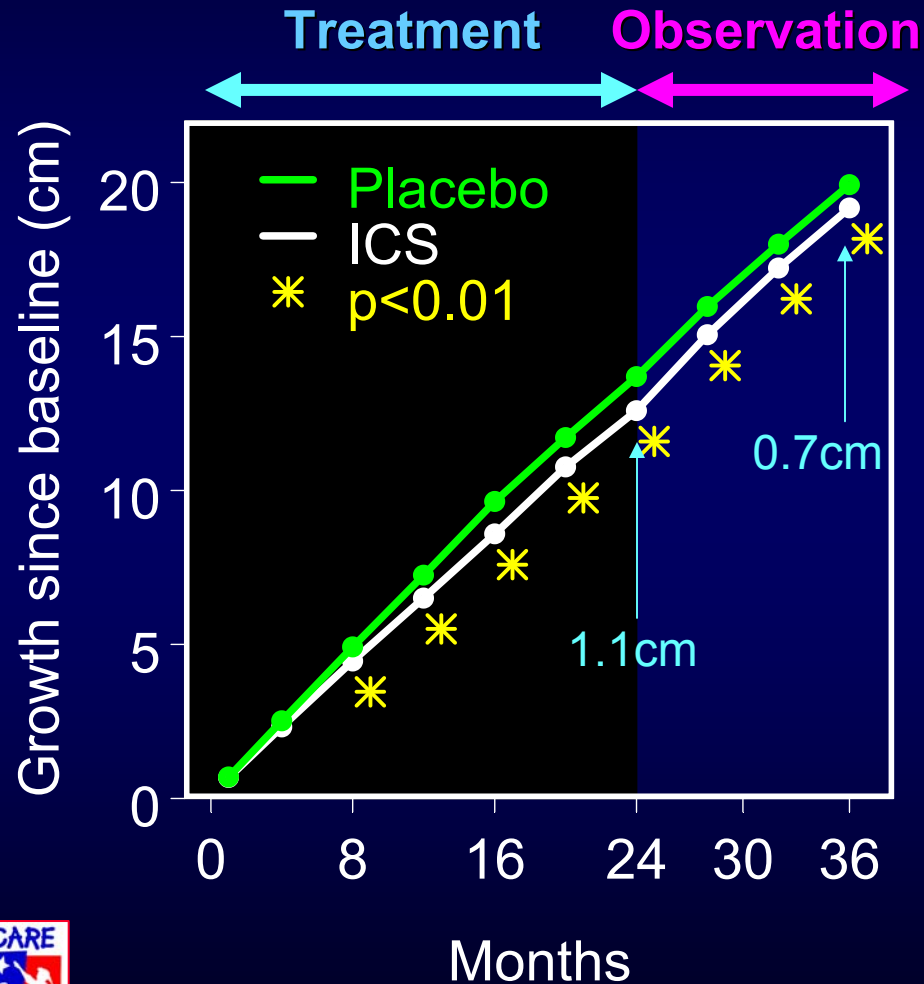
## Asthma Exacerbations



# Characteristics Associated with EFD Response

Stratifying Variable	Percentage of EFDs			P-value (ICS vs Placebo)
	ICS Mean (95% CI)	Placebo Mean (95% CI)	Difference (95% CI)	
Male	93 (92, 95)	86 (83, 89)	7.3 (3.9, 11.1)	0.0005
Female	92 (89, 94)	92 (89, 94)	0.1 (-3.4, 3.5)	0.9
Caucasian	93 (91, 95)	84 (80, 88)	9.1 (4.8, 13.9)	0.0001
Non-Caucasian	92 (89, 94)	93 (91, 94)	-1.0 (-3.9, 1.7)	0.6
Run-In EFD <80%	92 (90, 94)	84 (79, 87)	8.6 (4.2, 13.2)	0.0009
Run-In EFD ≥80%	93 (91, 95)	93 (91, 95)	0.0 (-2.5, 2.5)	0.9
ED/Hospitalization History	95 (93, 96)	87 (83, 90)	7.7 (3.9, 11.6)	0.0004
No ED/Hospitalization History	90 (87, 92)	91 (89, 93)	-1.1 (-4.4, 2.1)	0.6
≥1 Positive Aeroallergen Skin Test	93 (91, 94)	86 (83, 89)	6.5 (3.2, 10.0)	0.0027
Negative Aeroallergen Skin Test	93 (90, 95)	92 (89, 94)	0.9 (-2.5, 4.4)	0.6

# PEAK: Low Dose ICS Impacted Growth



	Height Percentile	
	End of treatment	End of observation
ICS	51.5%	54.4%
Placebo	56.4%	56.4%
p-value	0.0001	0.03



*Alternate Strategies to Reduce  
Morbidity Among Preschool  
Wheezers:*

**Does Episodic Therapy (OCS, ICS  
or LTRA) in Preschool Children  
with Recurrent Episodes of  
Wheezing Provide Clinical  
Benefit?**

# Oral Steroids Early in Illness

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- 32 children under 6 y/o with asthma typically provoked by viral URIs
- 2 year prospective non-randomized study
  - **Year 1:** Theophylline and metaproterenol PO, inhaled albuterol, prednisone if severe
  - **Year 2:** Prednisone at 1st sign of URI in an unblinded group
- During Year 2:
  - Prednisone group had fewer attacks, 65% fewer wheezing days, 61% ↓ ED visits, 90% ↓ hospitalization
  - Prednisone use at 1st sign of URI did not lead to greater prednisone use overall

**Conclusion:** Early prednisone may be effective in attenuating episodes of viral-induced wheezing.

**Problems:** Non-blinded. Non-randomized. Oral steroids prior to symptoms not widely accepted by practitioners.

# Oral Steroids Early in Illness

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- 233 1-5yr olds with prior hospitalization for “viral wheeze” which arose within 2 days of coryzal upper respiratory tract symptoms
- Double blind randomized trial
  - At the “start of the next episode of “viral wheeze”, begin:
    - Prednisolone 20mg qd x5 days OR Placebo
      - Continue for 5 days
    - Albuterol q4h as needed
- Primary outcome – 7 day mean daytime and nighttime symptom scores

# Oral Steroids Early in Illness

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## ➤ Findings:

- No difference symptom scores, albuterol use, hospitalization, or parental preference between the 2 groups.

## ➤ Conclusion:

- “No clear benefit of a short course of parent-initiated oral prednisolone for viral wheeze in children 1-5 years old (even in those with above average eosinophil counts).”

## ➤ Problems:

- Very high “dropout” rates – >50% in steroid group, 36% in placebo group.
- Very high rate of noncompliance – 68% of parents did NOT give the study medication or complete the diary cards during the next episode of viral wheeze.
- Low symptoms scores during episodes – mean <1 on a 0-3 scale.

# Inhaled Corticosteroids Early in Illness

	Age	N	Intervention	Outcomes
Wilson (1990)	1-5 yrs	24	BDP MDI 750 BID for 5 days vs. PLA	<b>ICS</b> – lower Sx scores, parental preference <b>No difference</b> – OCS use, hospitalization
Connet (1993)	1-5 yrs	32	BUD MDI 800 BID or 1600 BID for 7 days vs. PLA	<b>ICS</b> – less wheeze <b>No difference</b> – duration of Sx, terbutaline use
Svedmyr (1999)	1-3 yrs	55	BUD MDI 400 QID for 3 days, then 400 BID for 7 days vs. PLA	<b>ICS</b> – lower Sx scores, less cough, less sleep disturbance <b>No difference</b> – URI Sx scores, $\beta$ -agonist or OCS use, ED visits

# Intermittent ICS in Infants with Episodic Wheezing

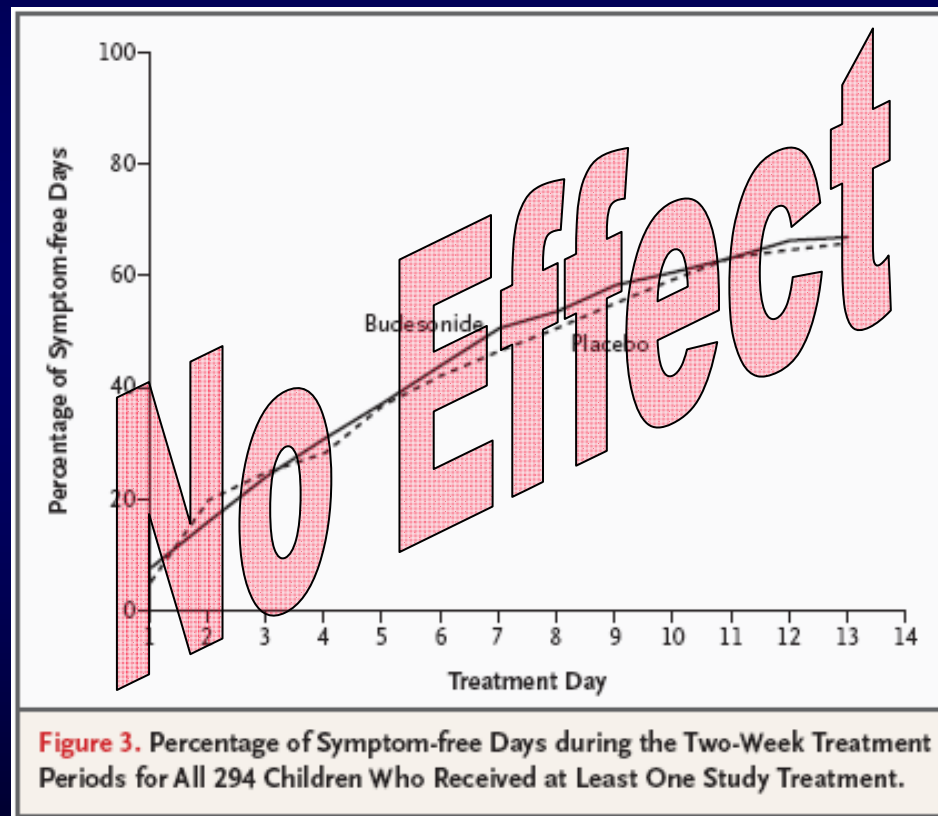
Copenhagen Prospective Study on Asthma in Childhood (COPSAC)

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- Prospective longitudinal birth cohort of 411 newborns with mothers with asthma enrolled at 1 month of age
- At first episode of wheezing (defined as any symptom affecting the child's breathing), randomized to:
  - Budesonide 400mcg/d or Placebo
  - *For 2 weeks after the 3<sup>rd</sup> day of symptoms*
  - Open label budesonide added for 2 weeks if persistent severe symptoms
- Followed for first 3 years of life

# Intermittent ICS in Infants with Episodic Wheezing

Copenhagen Prospective Study on Asthma in Childhood  
(COPSAC)



Budesonide 400mcg/d vs placebo for 2  
weeks after day #3 of symptoms

Bisgaard H et al. NEJM 2006;354:1990-2005

# Short-Course Montelukast for Intermittent Asthma in Children

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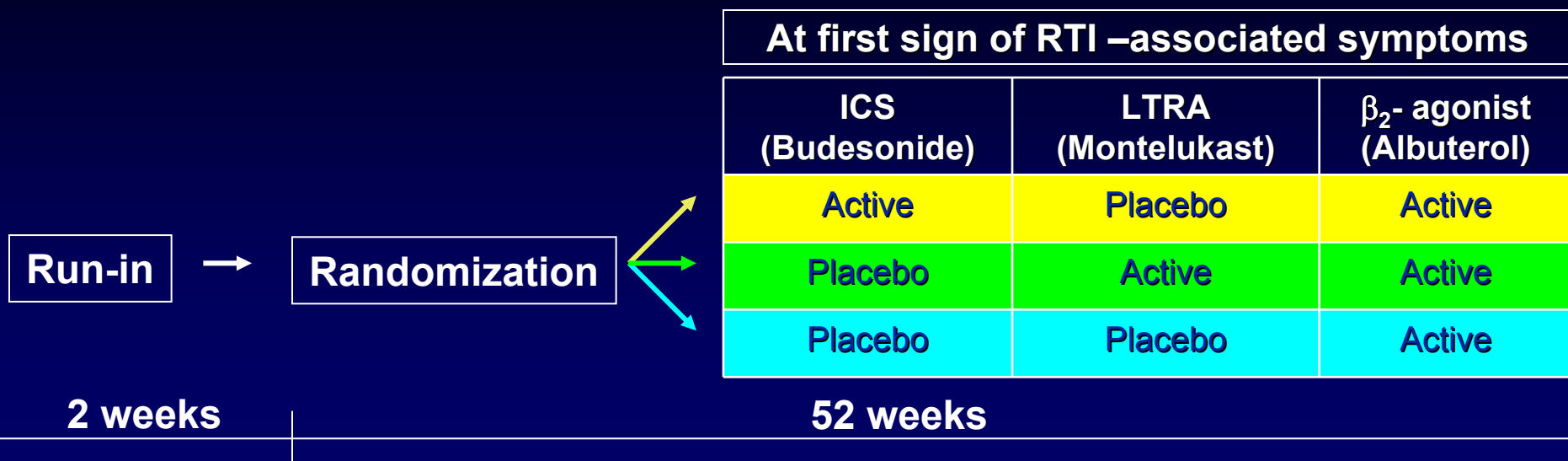
- 202 children 2-14 yrs of age with MD-diagnosed intermittent asthma, asymptomatic & no asthma medications between episodes
- 3-6 urgent visits/ED visit/hospitalization in past year
- Randomized double-blind, placebo controlled 12 month trial
  - Montelukast or placebo – to begin at onset of asthma symptoms or 1<sup>st</sup> sign of URTI in whom an URTI was usually followed by asthma & continued for  $\geq 7$  days or until symptoms had resolved for 48 hours (max 20 days). Maximum 5 episodes. All received  $\beta$ -agonists and oral steroids available.
- Primary outcome: Health care resource utilization for asthma
- Secondary outcomes: Indicators of episode duration & severity

# Short-Course Montelukast for Intermittent Asthma in Children

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- Montelukast group experienced:
  - 28.5% fewer health care resource utilizations (163 vs 228,  $p=0.007$ )
  - Lower total symptom scores during episode ( $p=0.049$ )
  - Lower absence from school ( $p<0.0001$ ) & parental work ( $p<0.0001$ )
- Groups were comparable:
  - Median # of puffs of SABA (median 36 puffs for each group)
  - Proportion of episodes requiring oral corticosteroids (20.5% for montelukast, 24.3% for placebo)
- Subgroup analysis (by age, gender, rhinitis, family history, # wheezing episodes, IgE level) did not identify subpopulations with differing response patterns

# AIMS: Study Overview



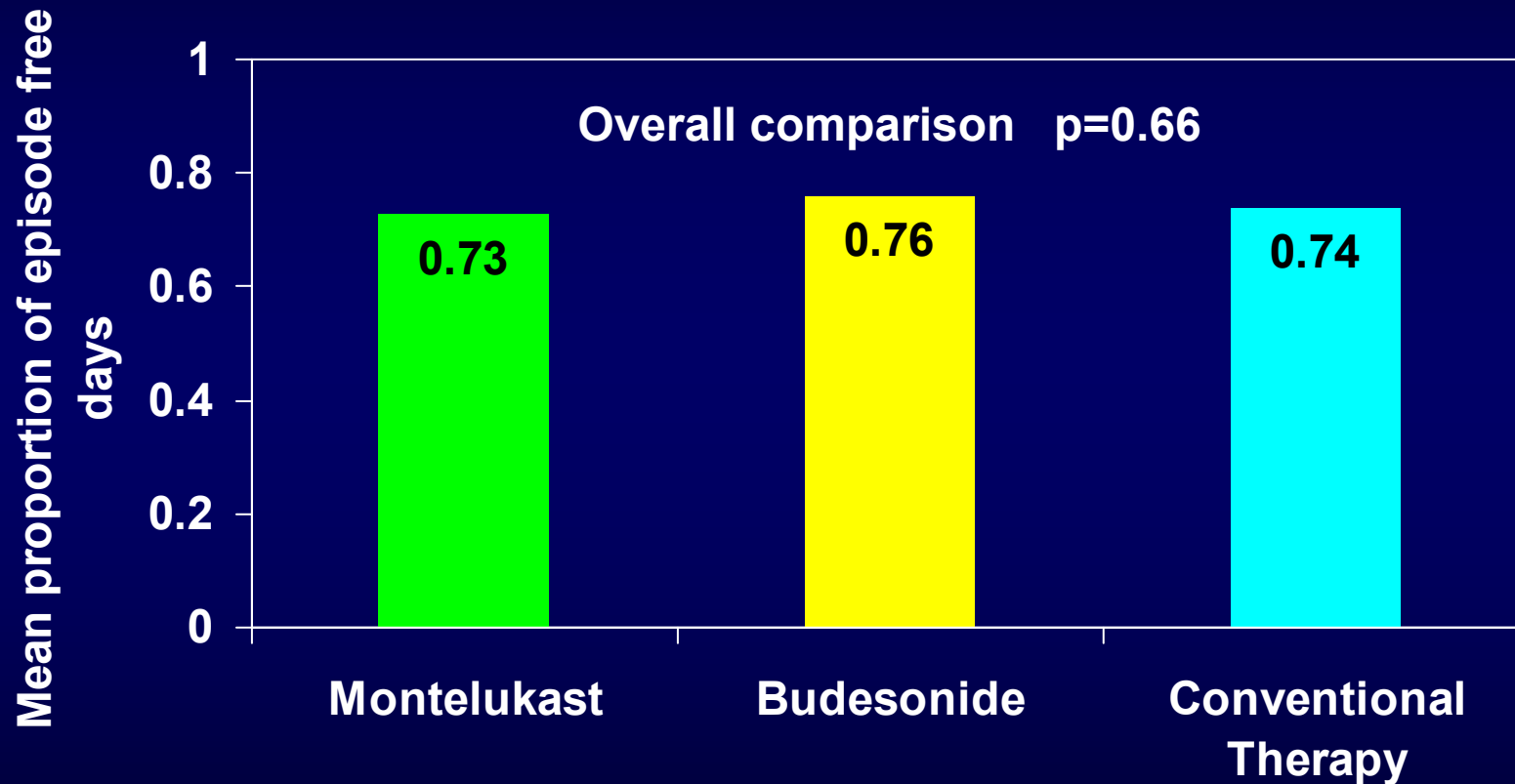
Drug	Dosing	Duration
Budesonide (Pulmicort Respules® - AstraZeneca)	1.0 mg twice daily	7 days
Montelukast (Singulair® - Merck)	4mg granules (12-23 months) 4 mg chewable tablets (24-59 months)	7 days
Albuterol - MDI or Nebulization Solution (Proventil® – Schering)	4 times daily, then as needed	2 days

# Inclusion Criteria

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1. Age 12-59 months
2. **Recurrent episodes ( $\geq 2$ ) of wheezing** in the context of a URI over the preceding 12 months
3. Either 2 episodes of **(a)**, OR 2 episodes of **(b)**, OR 1 episode of **(a)** AND 1 episode of **(b)** within the past 12 months:
  - a) Urgent care visit for wheezing which required treatment with at least a bronchodilator
  - b) Episode of wheezing which required treatment with oral corticosteroids

# AIMS Primary Outcome - Mean Proportion of Episode Free Days



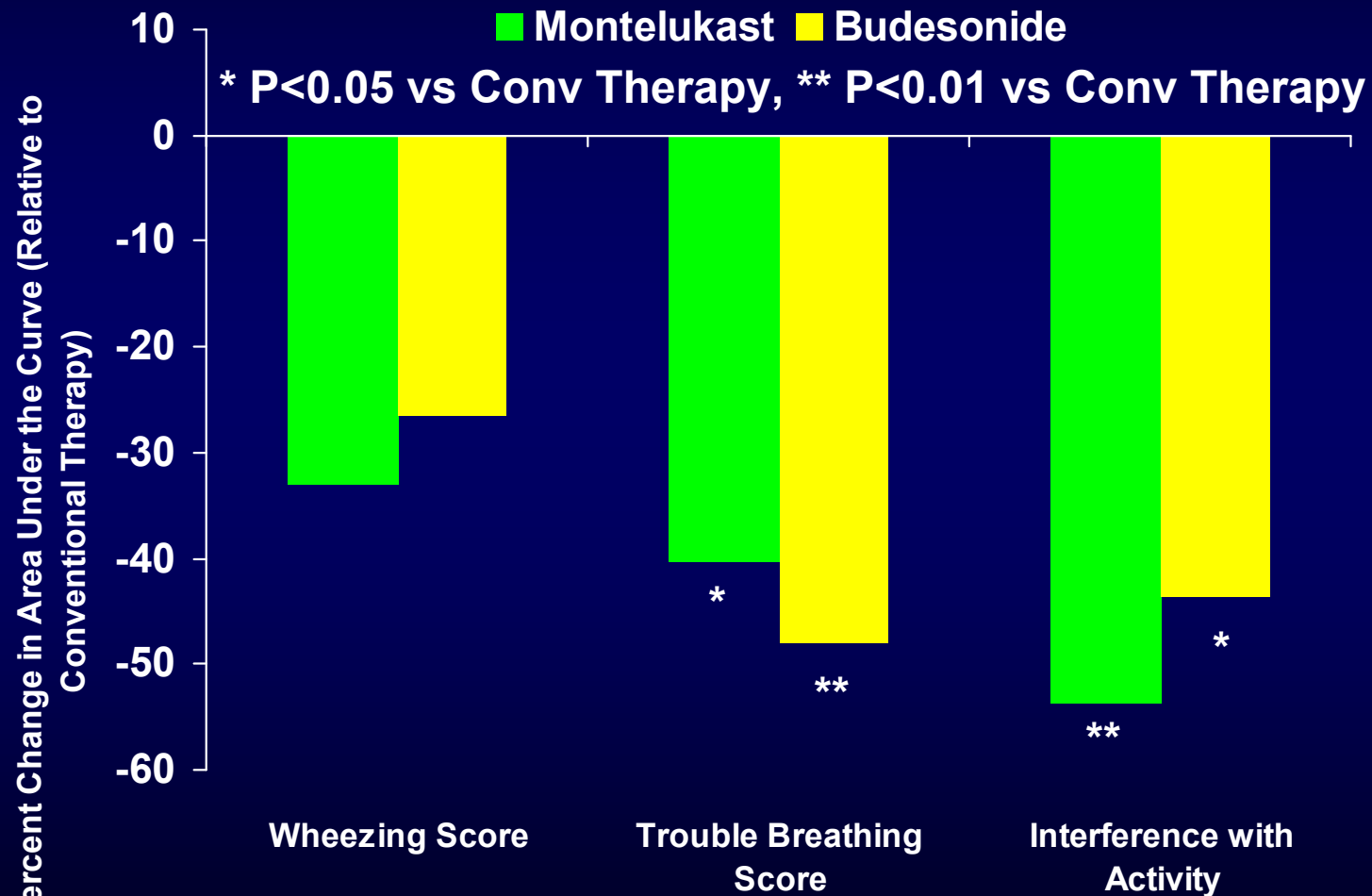
# AIMS: Secondary Outcomes

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- Treatments did not differ in terms of:
  - Prednisolone use
    - Number of courses
    - Time to first course
  - Time to treatment failure
  - Urgent care visits or hospitalizations
  - Days missed from daycare or parental work
  - Linear growth

# AIMS: Improvement in Symptoms Relative to Conventional Therapy

## *POSITIVE Asthma Predictive Index*



**Negative Asthma Predictive Index:** No significant effect of treatment on any symptom measure

Bacharier LB et al. J Allergy Clin Immunol 2008; 122:1127-35



# **Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children**

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- **Triple-blind placebo-controlled trial (n=129)**
- **1-6 yrs of age with 3 or more wheezing episodes (lifetime), seemingly triggered by URIs**
- **No intercurrent symptoms**
- **At least 1 course of oral corticosteroids in past 6 months (or 2 in past 12 mo)**
- **Exclusion of children with suspected allergic rhinitis or allergic sensitization to aeroallergen(s)**
- **At 1<sup>st</sup> sign of URI, parents began study drug (FP 750mg BID or placebo) until 48 hrs with no symptoms of cough or wheeze + albuterol as needed**
- **Primary outcome: group rate of oral corticosteroid use**

# Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children

Outcome	FP Group	Placebo Group	OR for FP Group
# URTI	521	526	
URTI requiring oral steroids	43 (8%)	93 (18%)	0.49 (0.3, 0.83)

- No difference in proportion of URTI associated with wheezing, cough, dyspnea or hospitalization
- FP associated with shorter duration of albuterol use

# Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children

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- FP group had significantly smaller increases in height (6.23cm vs 6.56 cm) and weight (1.53kg vs 2.17kg)
- No differences in basal cortisol level, bone mineral density, or adverse events

# Summary

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- Early childhood wheezing is common
- Multiple wheezing phenotypes which differ in natural history and response to therapies
- Optimal treatment strategy not yet defined, and likely dependent on many patient/disease characteristics