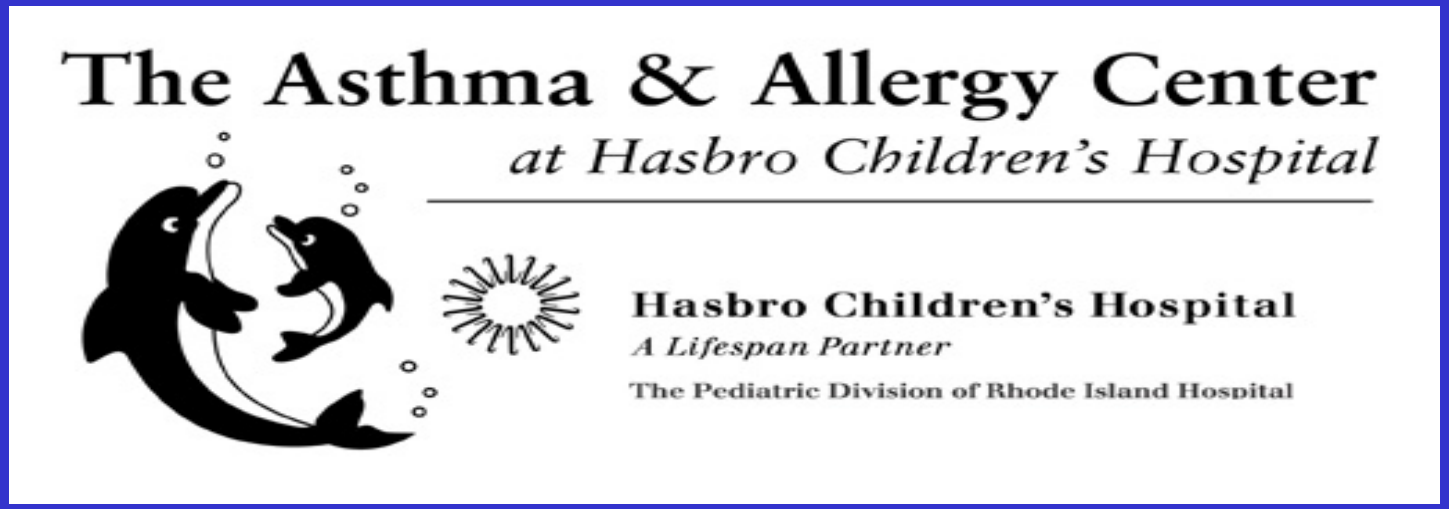
ASTHMA 2007

ASTHMA & GUIDELINES UPDATE



Robert B. Klein, MD

Director, Asthma and Allergy Center
Associate Pediatrician-in Chief and Medical Director HCH

Professor and Vice Chair of Pediatrics Brown Medical School

ASTHMA 2006

- Asthma Facts
- Bronchiolitis to Asthma to COPD ?
- Guidelines with preview
- New Issues?

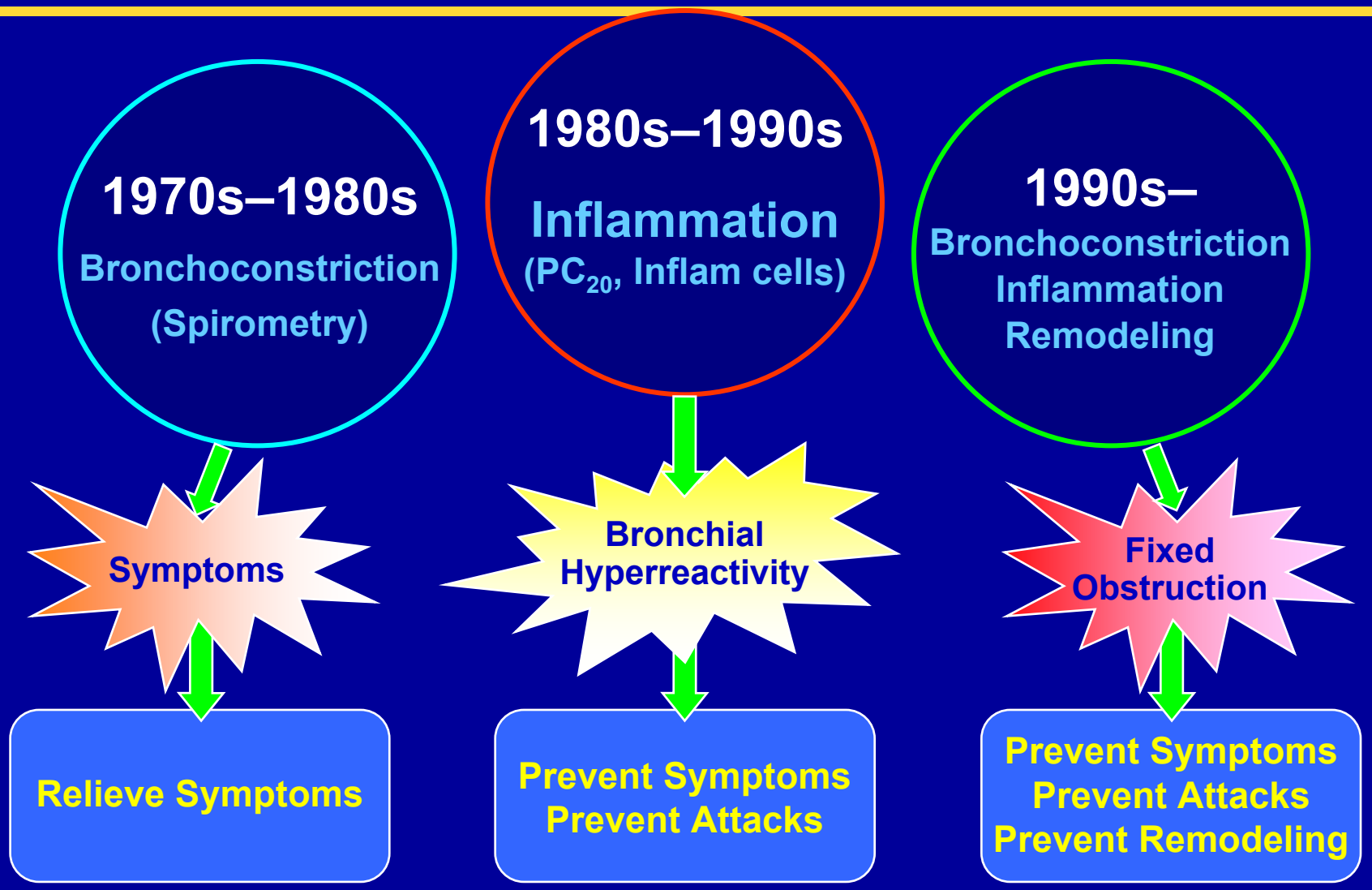
ASTHMA 2007

- Asthma Facts
- Guidelines Preview
- Severity v. Control
- Discussion

Magnitude of the Problem

- **150 million asthmatic world wide**
- **Prevalence increasing in most countries (20 to 50% every 10 years)**
- **Significant cause of school/work absence**
- **Health care expenditures very high**
- **1 million unnecessary deaths each decade**

Our Understanding of Asthma Has Evolved Since the 1970s

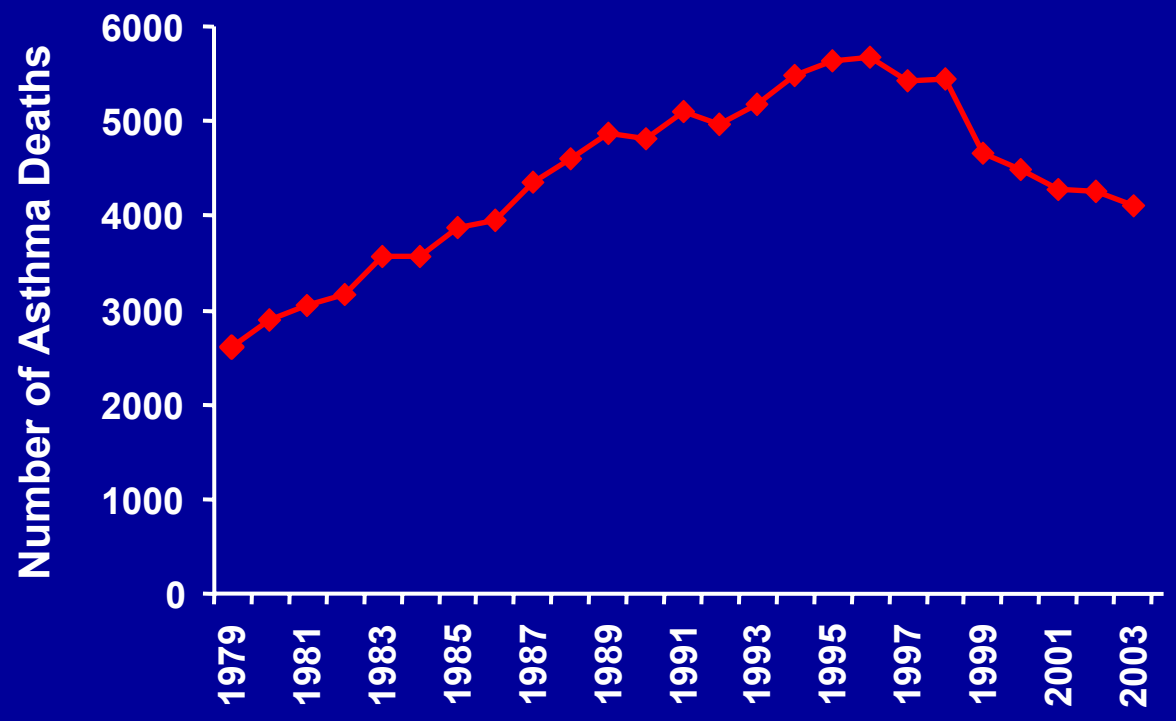


US Burden of Asthma in 2004

- Current asthma prevalence: 20.5 million Americans (6.2 million children)
- Annual burden of illness:
  - 497,000 hospitalizations annually
  - 1.8 million ED visits annually
  - Approximately 4000 deaths per year in 2003
  - 14 million lost school days in children and 14.5 million lost workdays
  - $16.1 billion in health costs annually

American Lung Association Epidemiology & Statistics Unit Research Program Services. *Trends in Asthma Morbidity and Mortality*. July 2006. Available at: www.lungusa.org. Accessed November 2, 2006.

in US Has Been Declining



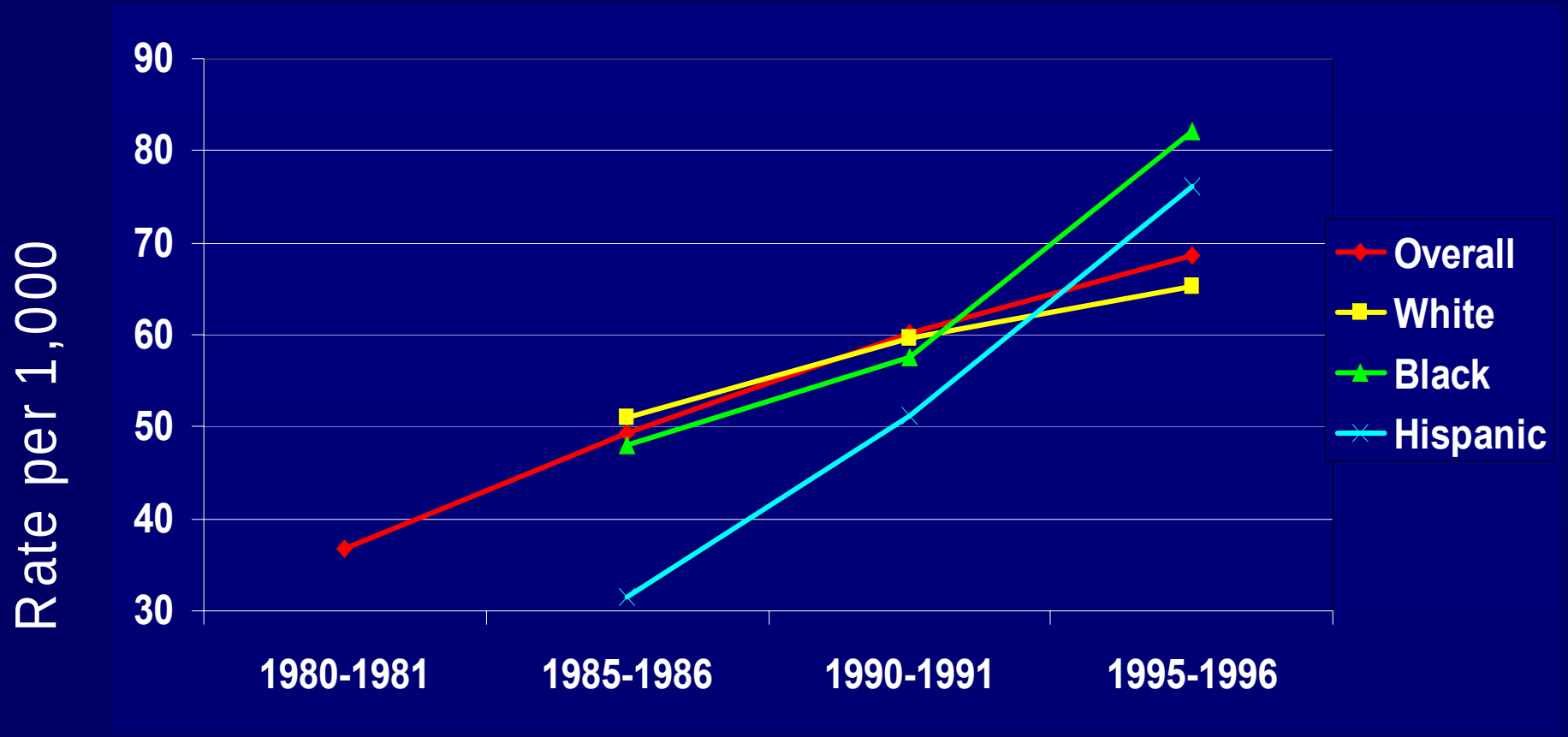
* 1979-1998 rates reflect the International Classification of Disease (ICD) 9th Revision Code 493. 1999-2003 rates reflect the ICD 10th Revision Codes.

American Lung Association Epidemiology & Statistics Unit Research Program Services. *Trends in Asthma Morbidity and Mortality*. July 2006. Available at: www.lungusa.org. Accessed November 2, 2006.

Asthma in Rhode Island

- Asthma is a statewide issue
  - RI: 10.7% childhood lifetime asthma prevalence
  - Estimated at 40,000 RI Children
- Greater impact in core cities
  - Childhood hospitalization rate, 1998-2002
    - 2.8 per 1000 for RI; 4.1 per 1000 for core cities
    - Woonsocket: 3.8 per 1000 children
    - Pawtucket: 3.0 per 1000 children
    - Providence: 4.9 per 1000 children

Average Annual Asthma Prevalence in US 1980 – 1996 in Children Younger than 18 years



Akinbami, L. et al. Pediatrics 2002;110:315-322

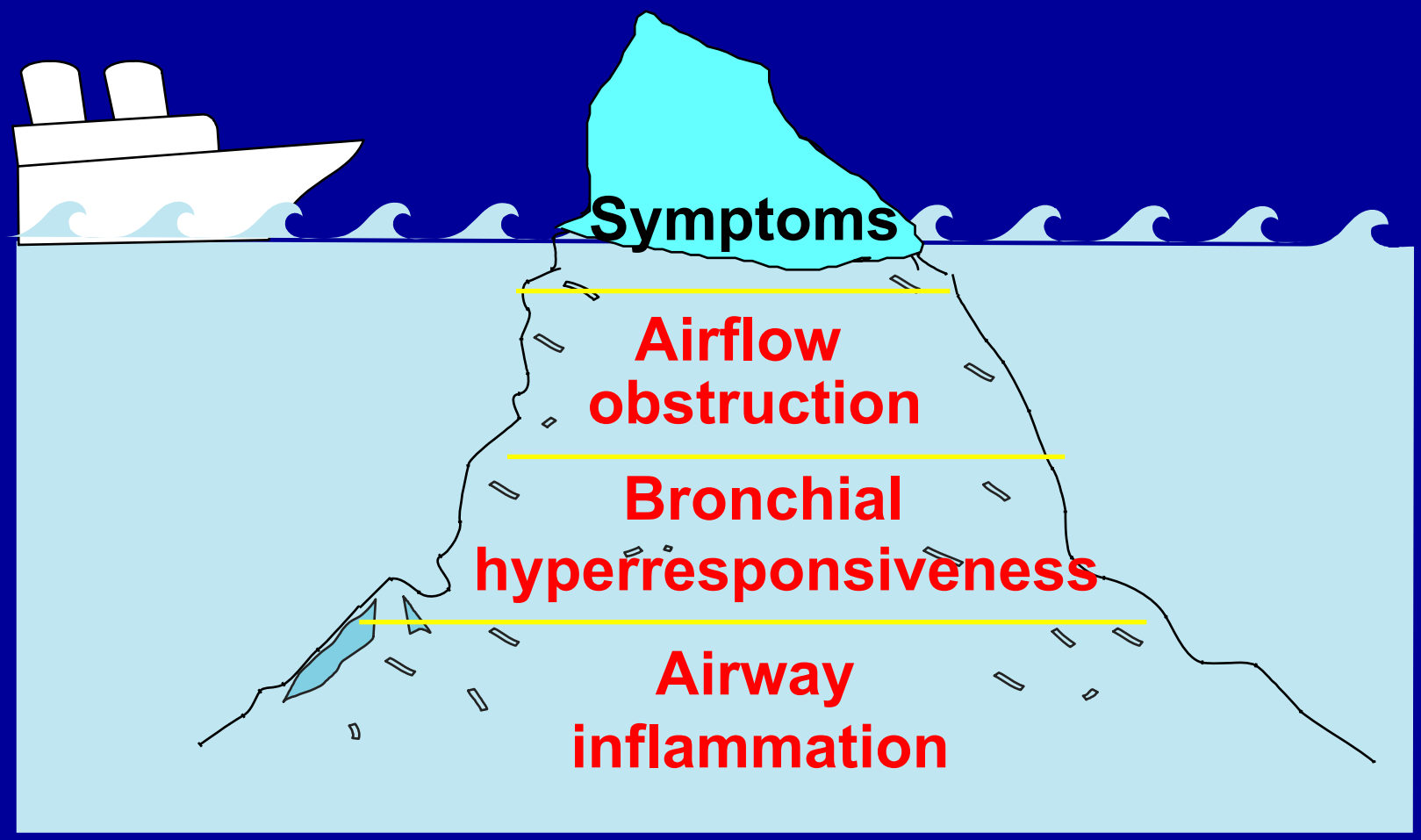
What Is Asthma?

Asthma Is a Chronic Inflammatory Disorder

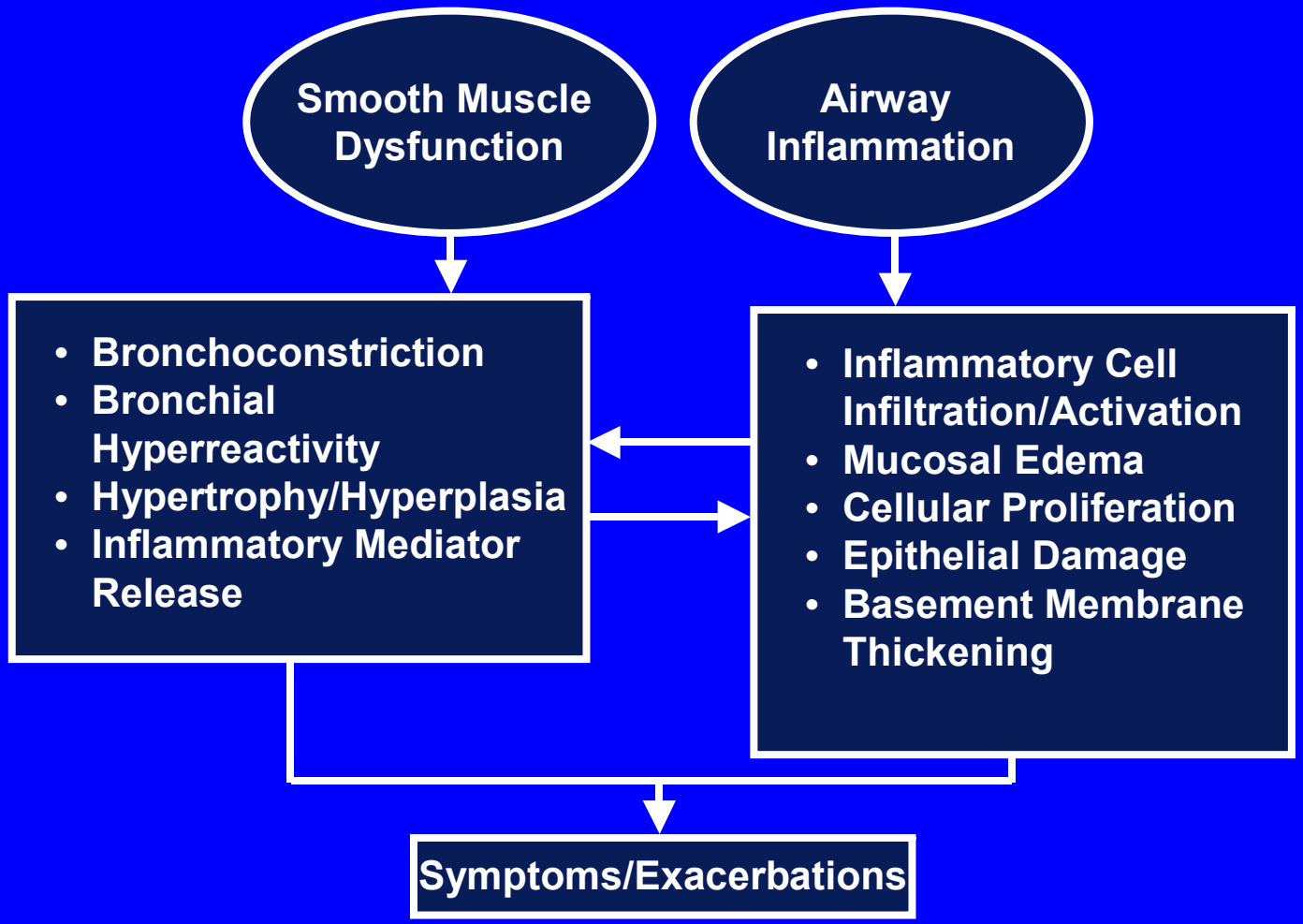
- Airway Inflammation leads to:
  - **Hyperresponsiveness** – response to triggers
  - **Obstruction** – usually at least partially reversible
  - **Symptoms** – cough, wheeze, dyspnea
- Symptoms are easily appreciated, but NOT the fundamental aspect of asthma

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

A Lot Going On Beneath The Surface



Asthma Pathophysiology



IV. Cough, Wheeze, Whistle, Gasp! Hey, What's going *on*?

Asthma in early childhood

Asthma is diff
of an infant de
asthma attack

How do No

Lungs allow a
exchange for
need. As air p
nose and mou
warmed and
hurting the de
airways. The
trap large part
molds, bacteri
(smoke, spray
cause serious

The air then g
airways. These
a tree, so that
millions of sm
oxygen to tiny
alveoli, where
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is coa
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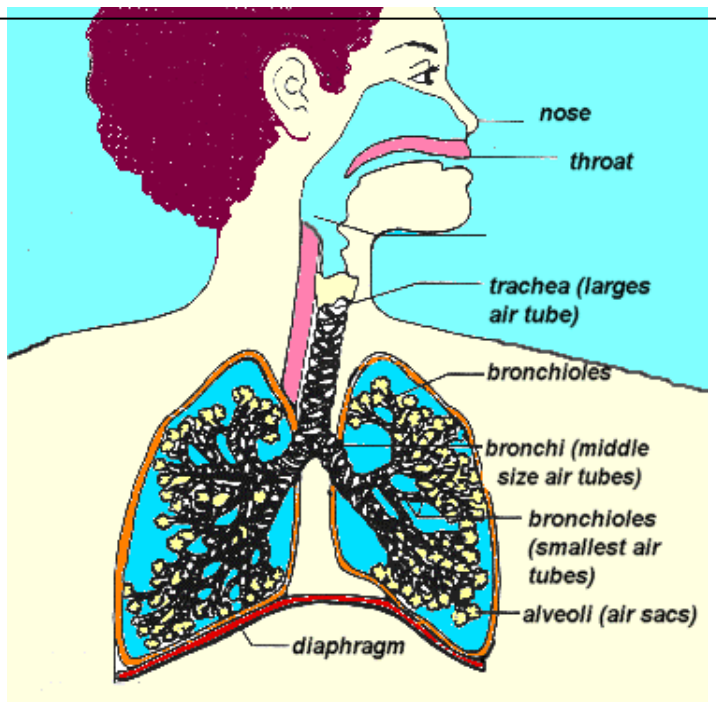
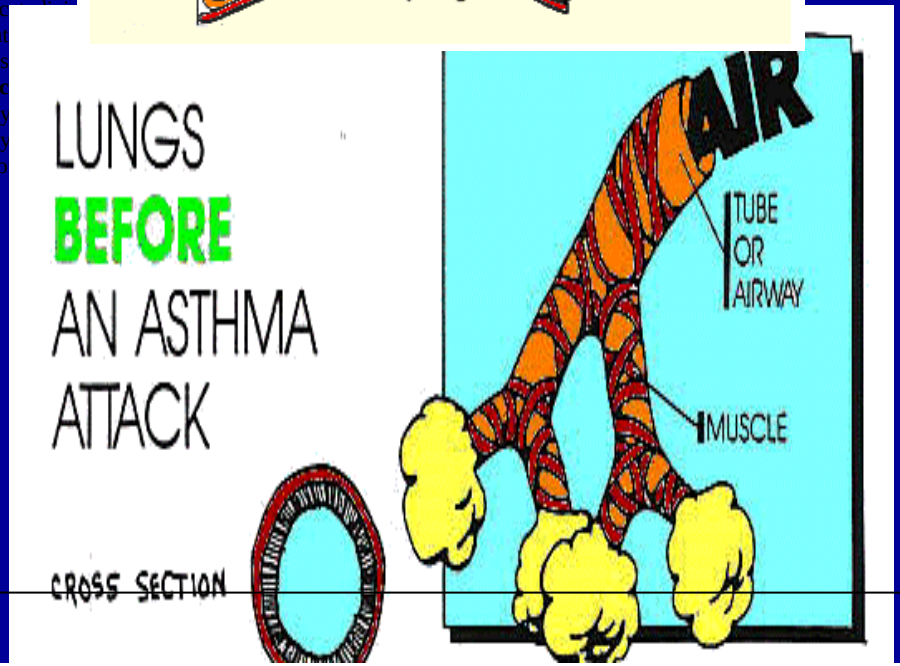


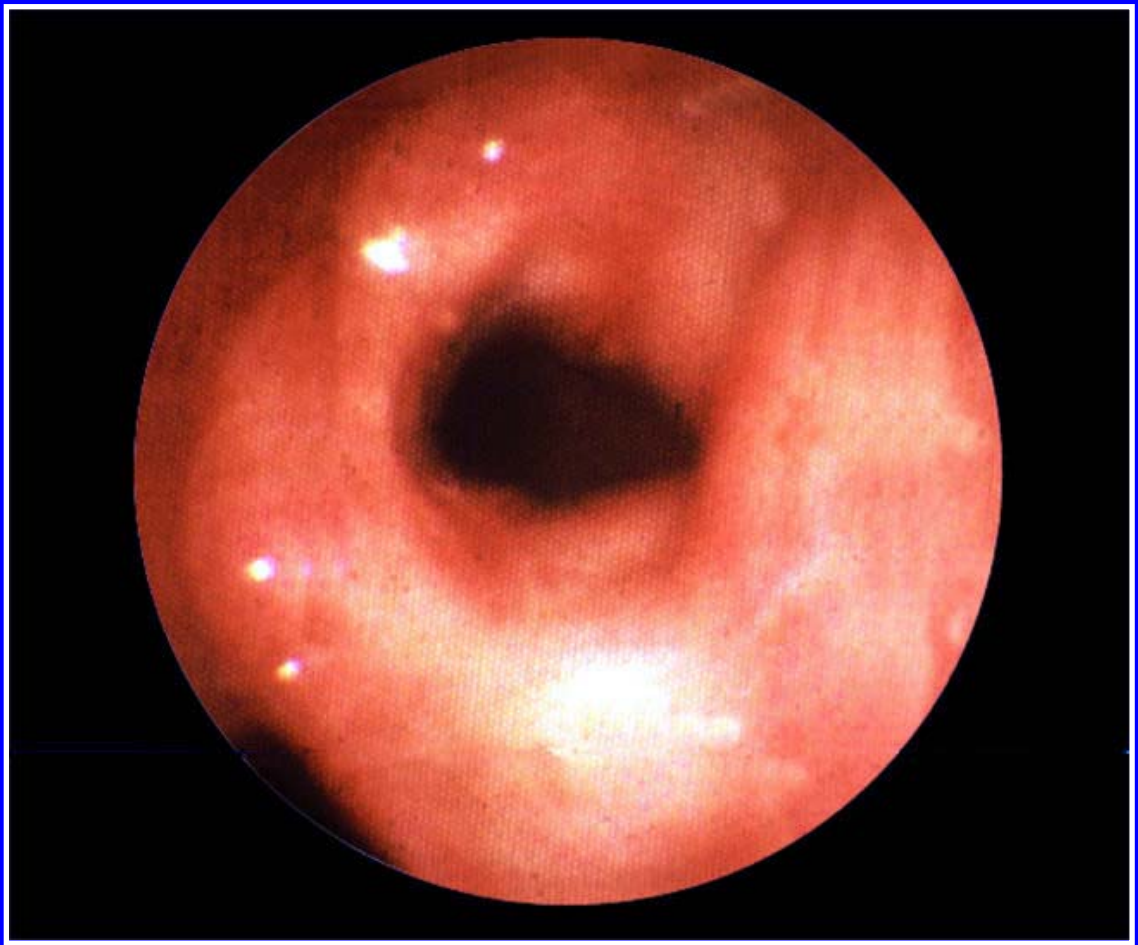


Bronchoconstriction

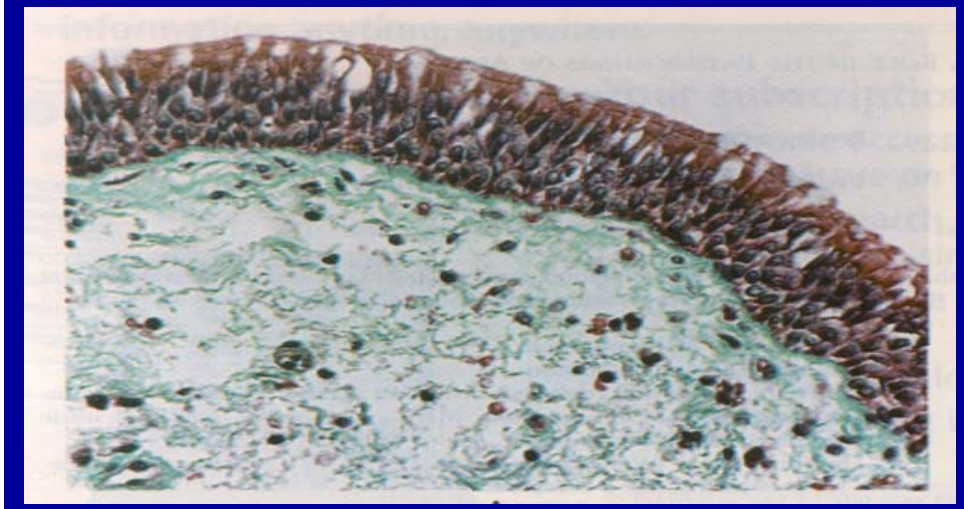
Before

10 Minutes After Allergen Challenge

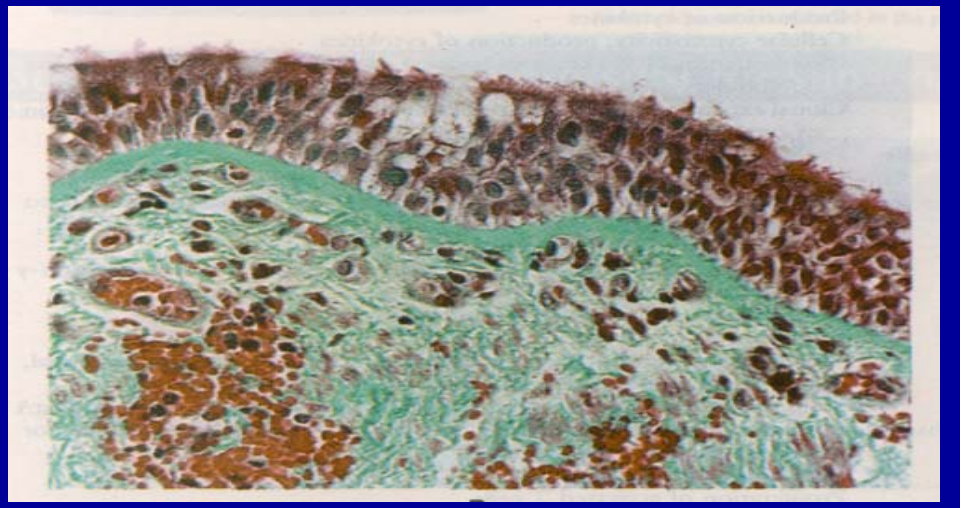
Airway Mucosal Edema



Inflammation in Mild Asthma



Subject Without Asthma

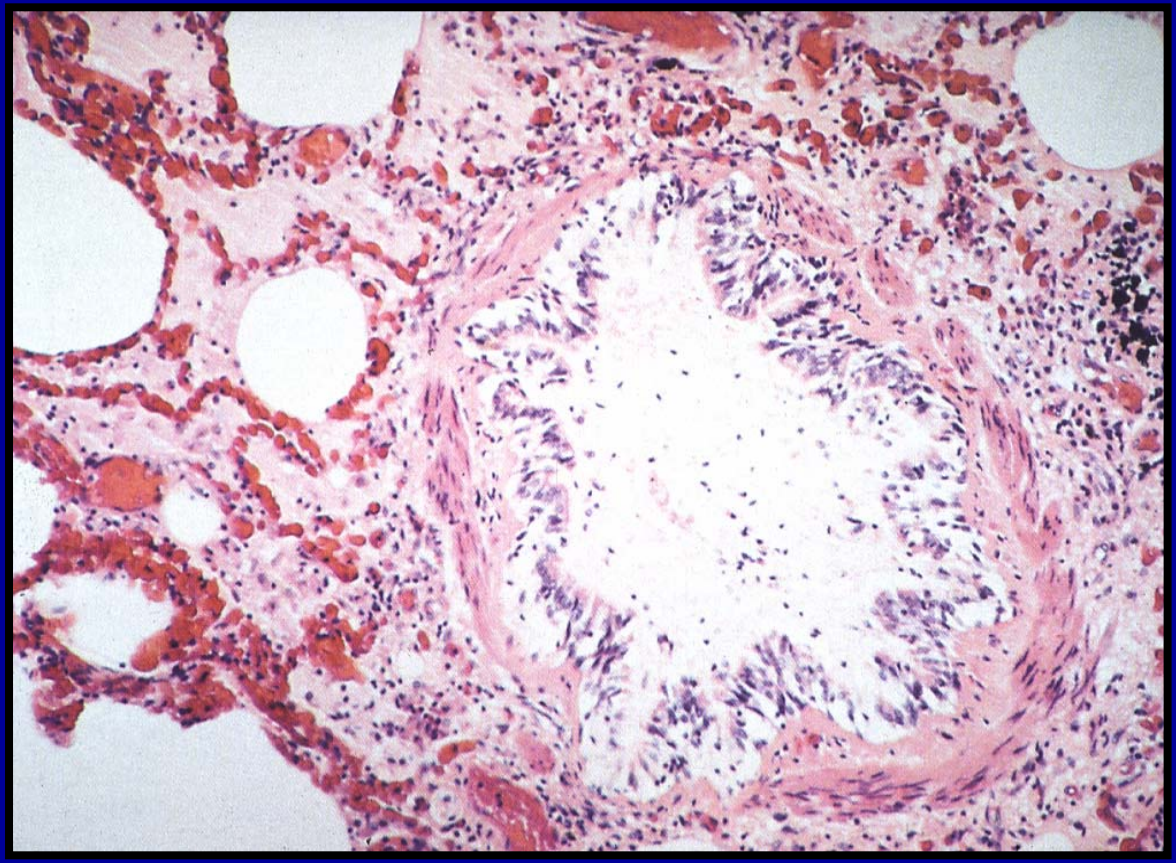


Patient With Mild Asthma

Specimen of Bronchial Mucosa

Busse and Lemanske. *N Engl J Med.* 2001;344:350-62.

Asthma

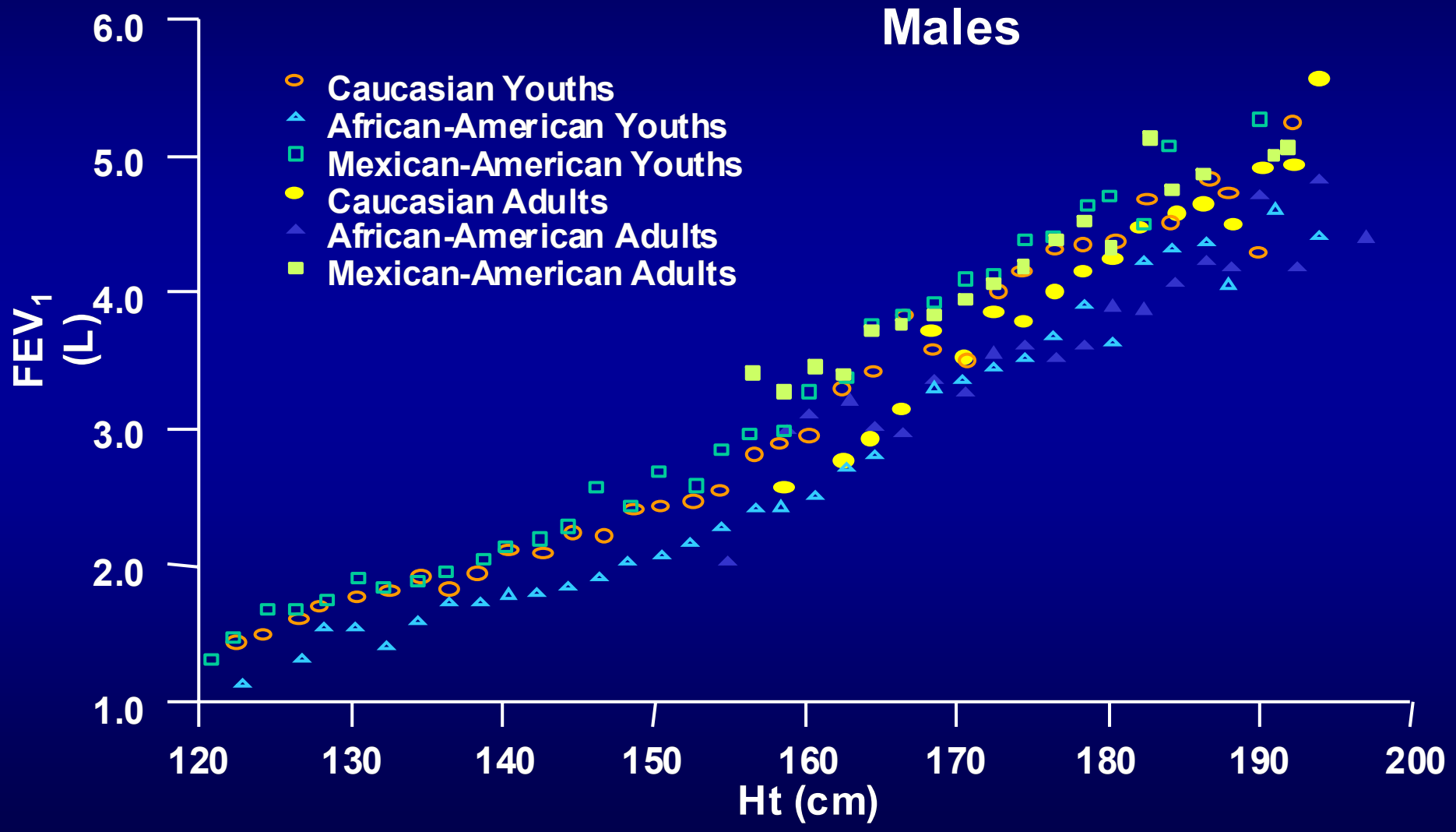


TUSCON CHILDREN'S RESP
LONGITUDINAL STUDY- 16 YRS

- **4 PHENOTYPES**
  - No wheeze
  - Transient: Wheeze with LRI before age 3
  - Late-onset: Wheeze at age 6 only
  - Persistent: Wheeze before age 3 and after 6
- Transient & Persistent had lower PFT's
- No significant changes compared to peers 6-16
- **Loss of Lung function appears to occur in first 6 years**

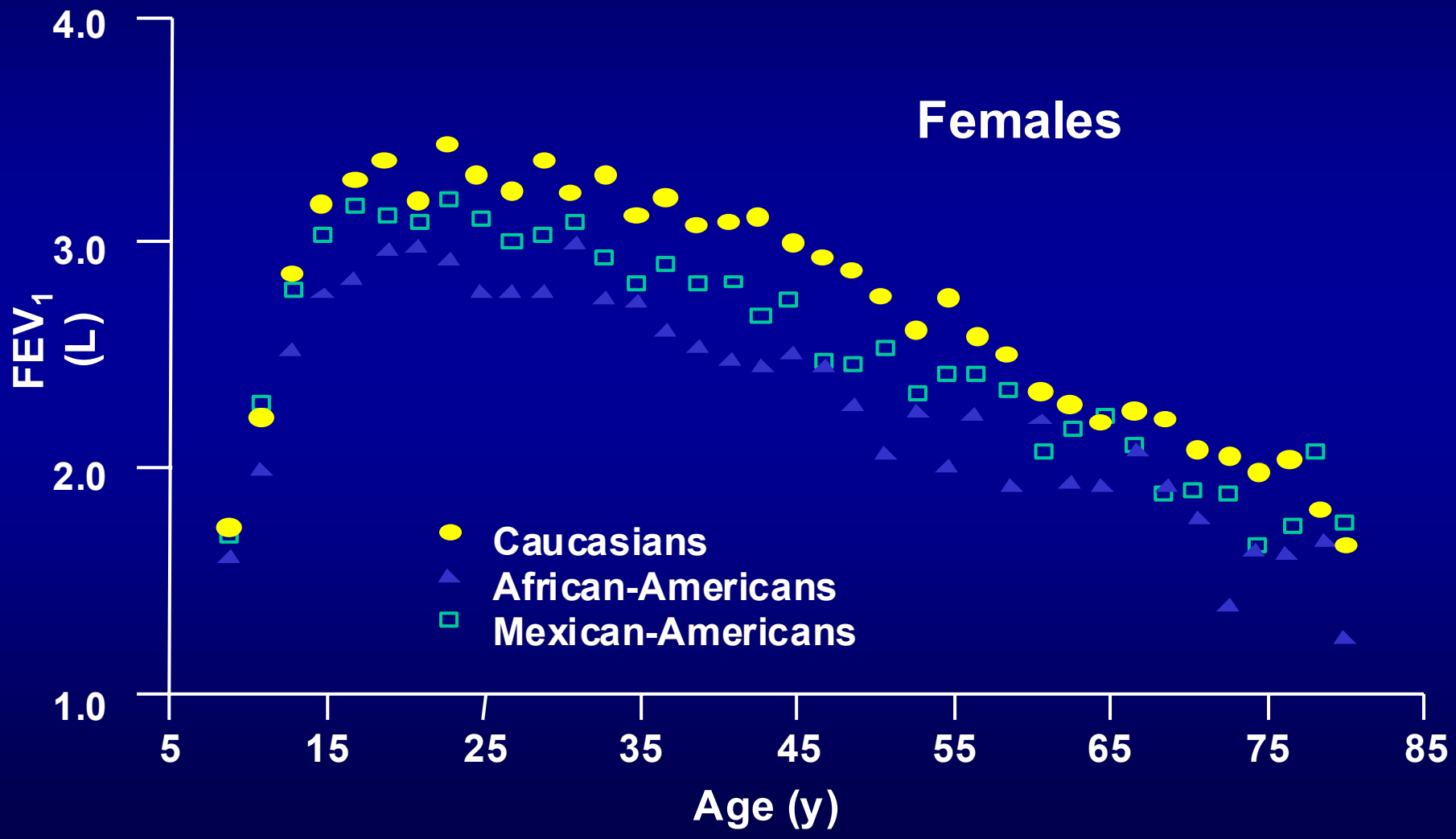
Morgan, AJRCCM, 2005; 172:1253

FEV_1 vs Height



Hankinson et al. *Am J Respir Crit Care Med* 1999;159:179-87.

FEV_1 vs Age



Hankinson et al. *Am J Respir Crit Care Med* 1999;159:179-87.

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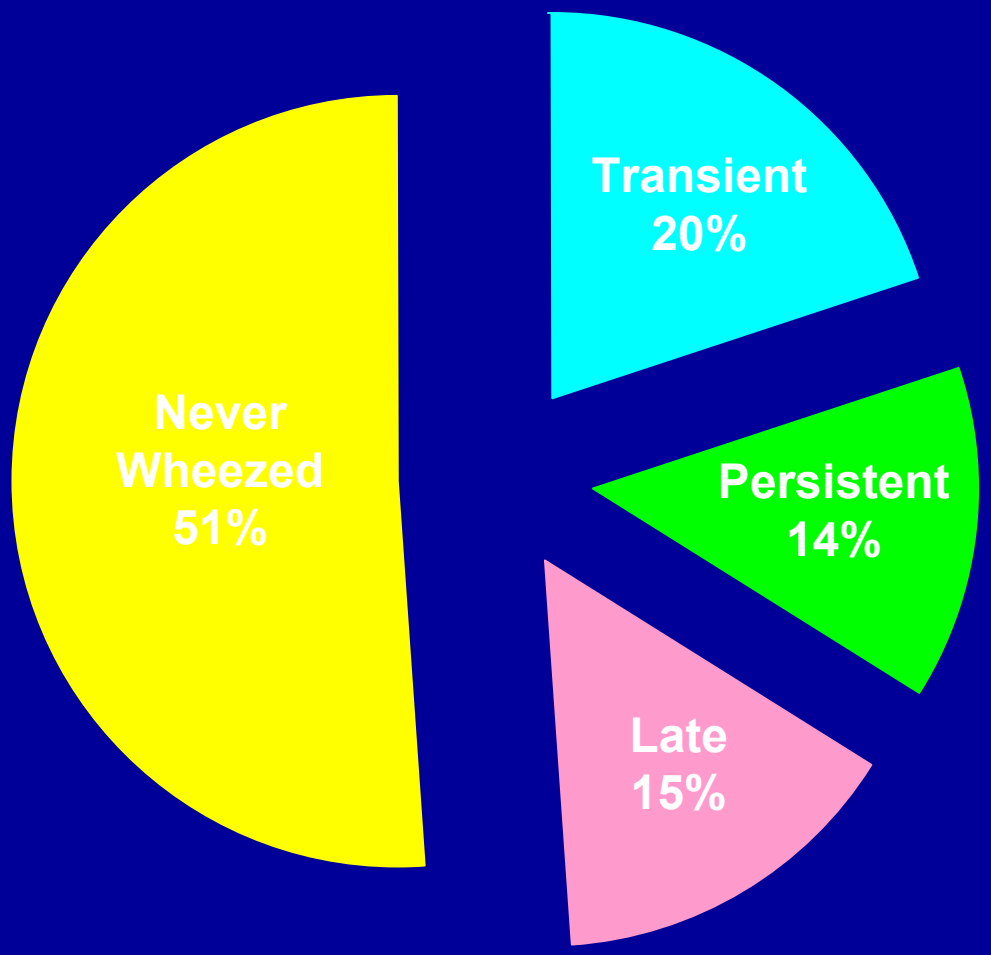
Asthma and Wheezing in the First Six Years
Tucson Children's Respiratory Study

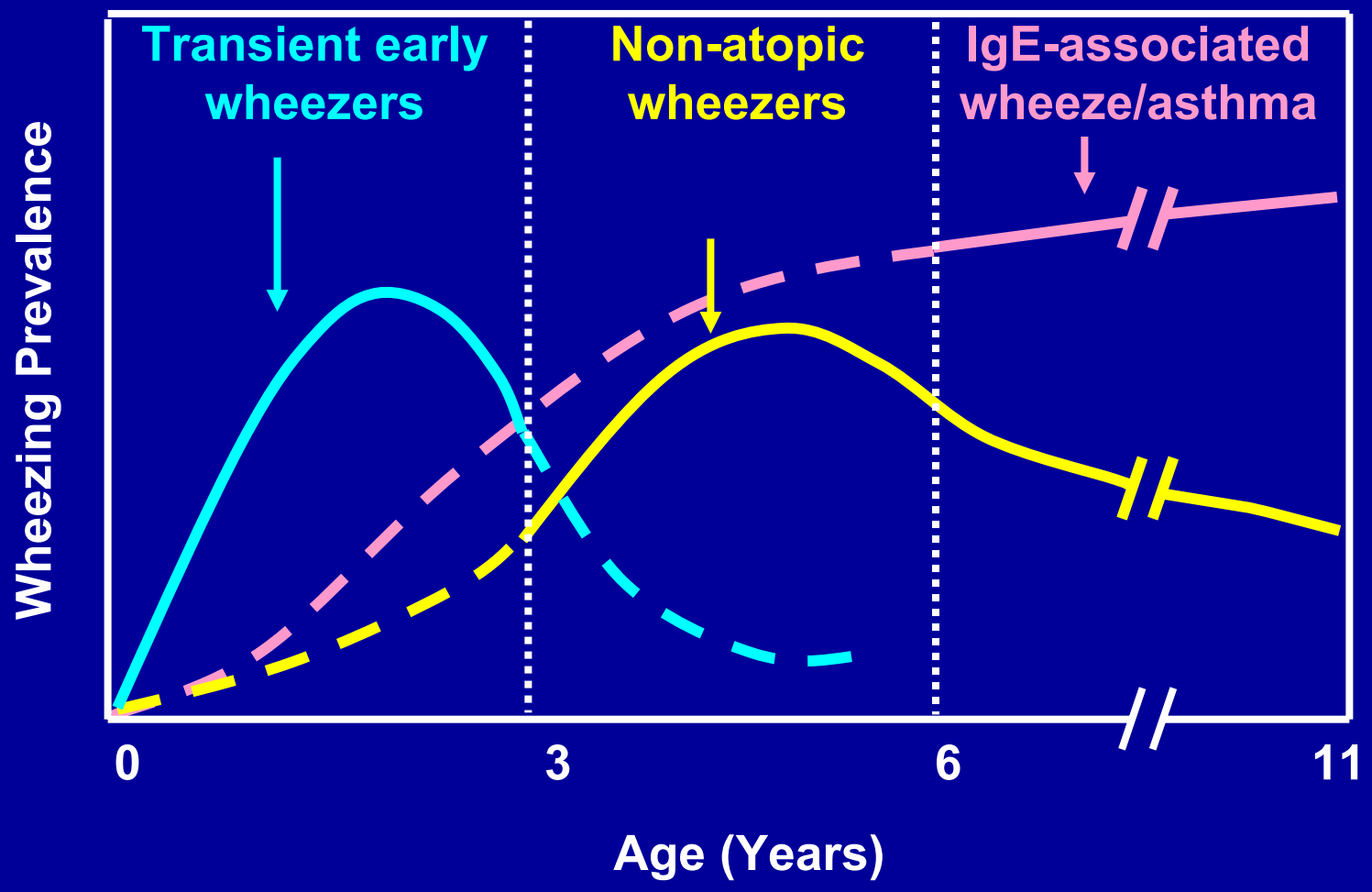


- **Transient:** wheeze <3 y, no wheeze at 6 y
- **Persistent:** wheeze <3 y, wheeze at 6 y
- **Late:** no wheeze <3 y, wheeze at 6 y
- **Never wheezed** by age 6 years

Martinez et al. *N Engl J Med* 1995;332:133-138.

Total n=826

Natural History of Pediatric Asthma



Martinez. *J Allergy Clin Immunol* 1999;104:S169-S174..

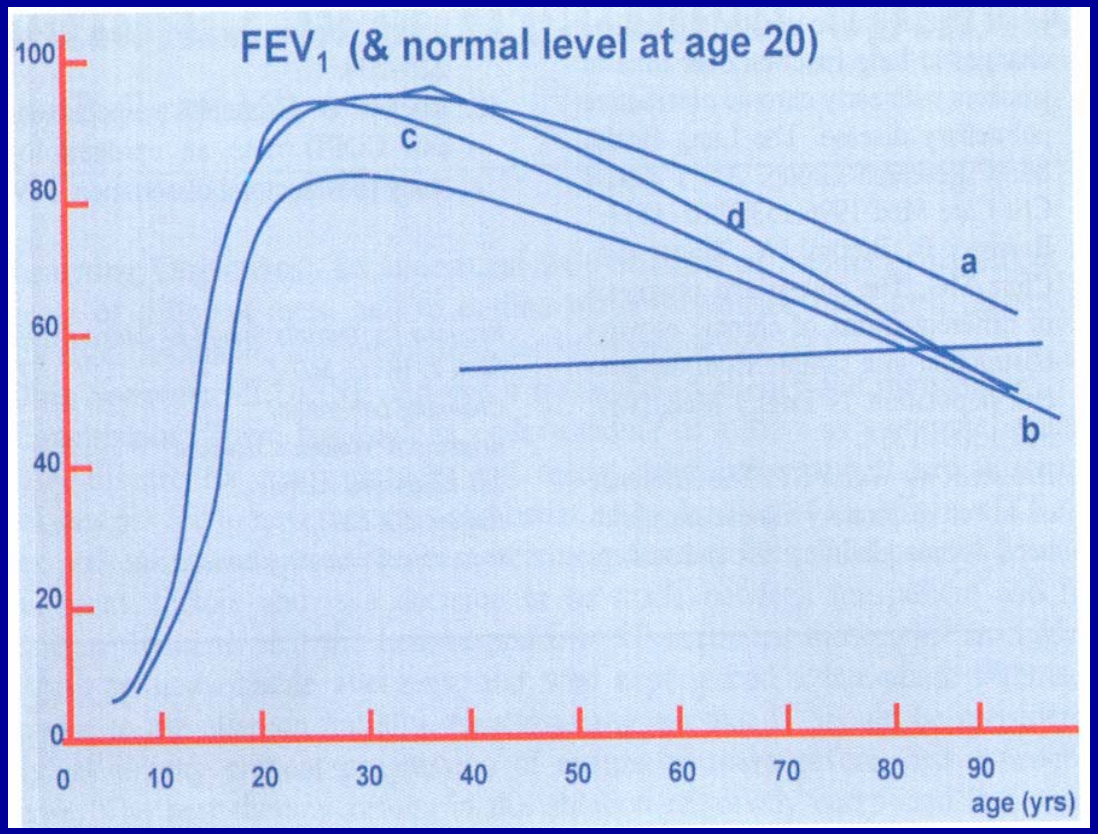
Growth and Decline of FEV_1

There are three ways to reach a low level:

1) **Decreased maximal growth**

2) **Premature decline**

3) **Accelerated decline**



Rijken B. Bronchial responsiveness and COPD risk: an epidemiologic study (postdoctoral dissertation, 1991).

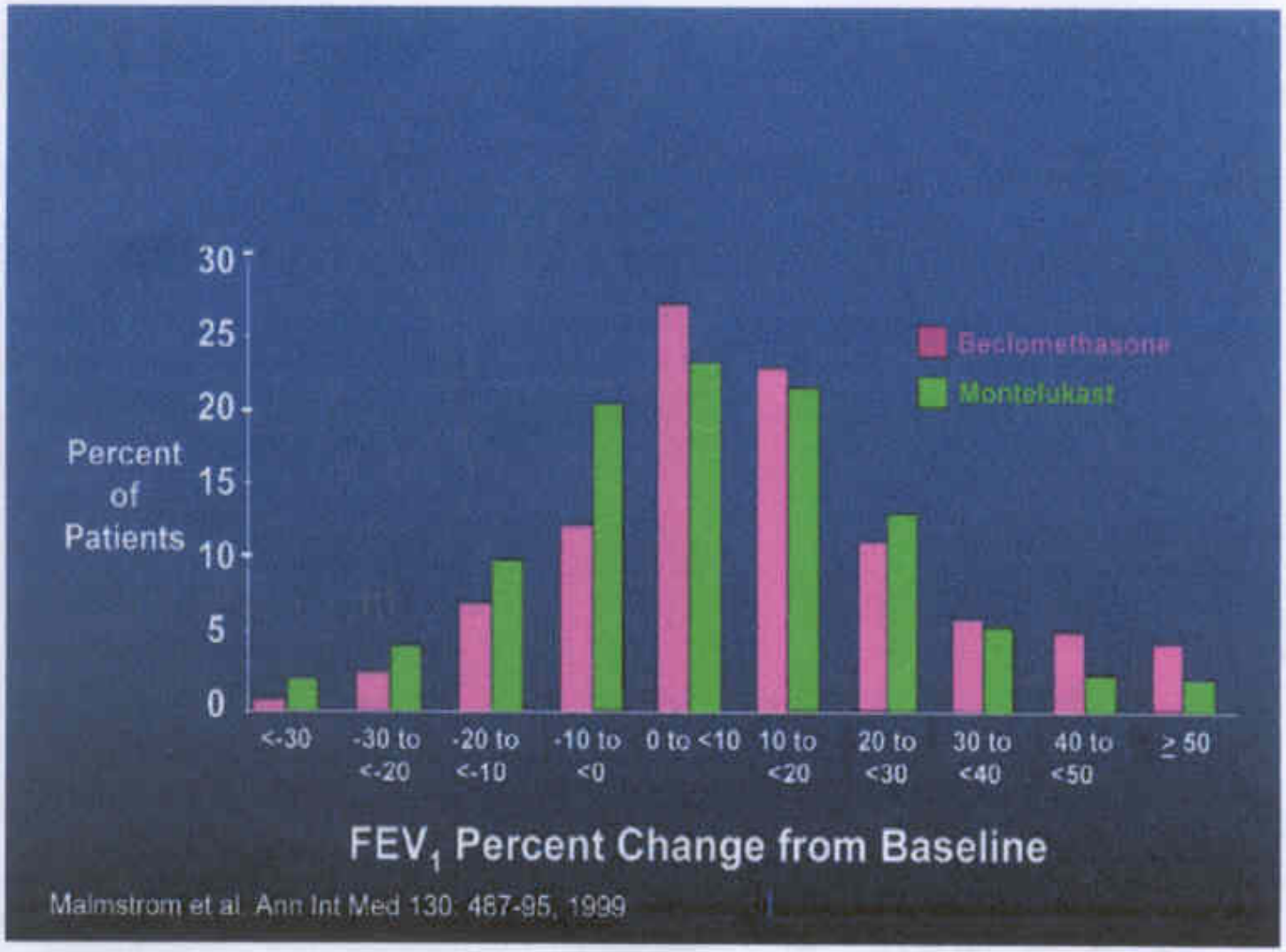


FIG 1. Distribution of patients experiencing a particular change in FEV_1. *Green bars* represent patients receiving montelukast, 10 mg once daily; *pink bars* represent patients receiving inhaled beclomethasone, 200 μg twice daily. Adapted with permission from Malmstrom et al. *Annals of Internal Medicine* 1999.[1]

GAP

ASTHMA 2006

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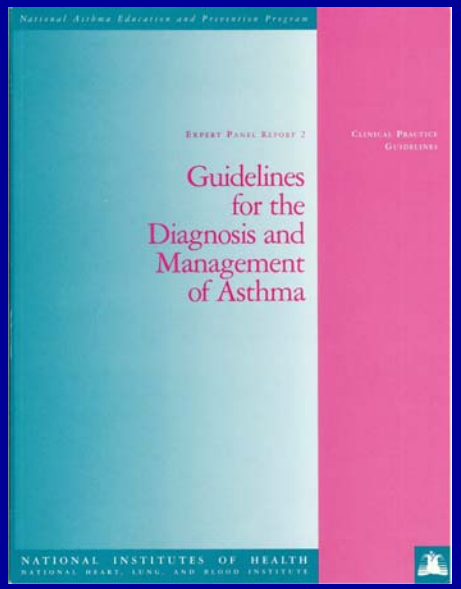
Timeline

Original Guidelines Through Update on Selected Topics 2002

Evidence from the medical literature

1991



1997

2002

Levels of Evidence: Categories A and B

- Evidence Category A
  - Randomized controlled trials (RCTs)
  - Rich body of data
- Evidence Category B
  - RCTs
  - Limited body of data

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

Methods for Collecting Evidence

- NAEPP guidelines provide evidence levels based on 2 reviews of the literature
- Reviews were evaluated and the level of evidence was categorized for each question
  - SRE-evidence
    - Systematic review of the evidence by the Agency for Healthcare Research and Quality Evidence-Based Practice Center
  - Evidence
    - Review of additional literature identified by the NAEPP Expert Panel

NAEPP = National Asthma Education and Prevention Program; SRE = systematic review of the evidence.

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

Levels of Evidence: Categories C and D

- Evidence Category C
  - Nonrandomized or uncontrolled trials
  - Observational studies
- Evidence Category D
  - Panel consensus judgment
  - Clinical literature insufficient to meet the criteria for categories A through C
  - Provision of guidance based on clinical experience or knowledge

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

NAEPP Step 2 Update: Treatment of Mild Persistent Asthma in Children Aged ≤5 Years

1997 Recommendation	2002 Recommendation
Daily anti-inflammatory medication. *Either:* Cromolyn (nebulizer preferred or MDI) or nedocromil (MDI) (infants and young children usually begin with a trial of cromolyn *or* nedocromil) *or* Low-dose ICS (with spacer/holding chamber and face mask)	Low-dose ICS (with nebulizer *or* MDI with holding chamber with or without face mask *or* DPI)

DPI = dry-powder inhaler; ICS = inhaled corticosteroid; MDI = metered-dose inhaler; NAEPP = National Asthma Education and Prevention Program.

NAEPP. *Guidelines for the Diagnosis and Management of Asthma 1997*. Publication no. 97-4051; NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

How Do We Classify Asthma?

NHLBI asthma guidelines, EPR-3

"641 pages down to 40 slides"

What's new, and can we use it?

Review by Cynthia Esteban

NHLBI Outline, 641 pages:

I. Natural History
II. Component 1: Asthma Assessment and Monitoring
III. Component 2: Control of Environment/ Comorbidity
IV. Component 3: Education for Partnership
V. Component 4: The Medications
VI. Managing Asthma Long Term
   A. 0-4 and 5-11 years old
   B. ≥12 years old
VII. Managing Special Situations
VIII. Managing Exacerbations

Clinical Features of Asthma Before Treatment

			Adults or Children Older Than 5 Years	
Classification	Days With Symptoms	Nights With Symptoms	FEV_1 or PEF (% Predicted Normal)	PEF Variability
Severe persistent	Continual	Frequent	≤60%	>30%
Moderate persistent	Daily	>1/wk	>60 to <80%	>30%
Mild persistent	>2/wk but <1/d	>2/mo	≥80%	20 to 30%
Mild intermittent	≤2/wk	≤2/mo	≥80%	<20%

FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow.

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

Asthma Severity and Treatment

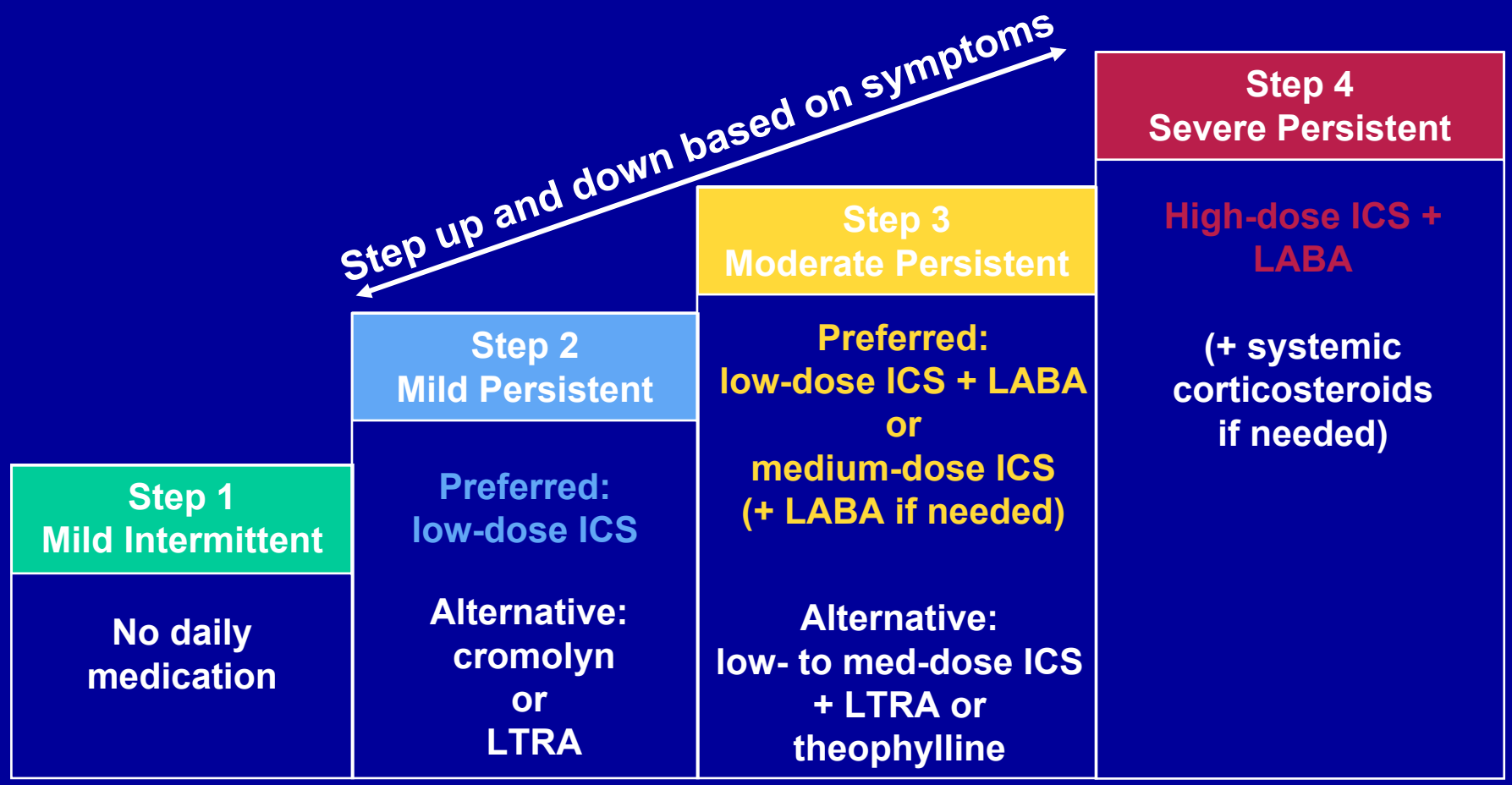
- Mild persistent
- Moderate persistent
- Severe persistent

} Daily controller medications

- Mild Intermittent } PRN medications

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

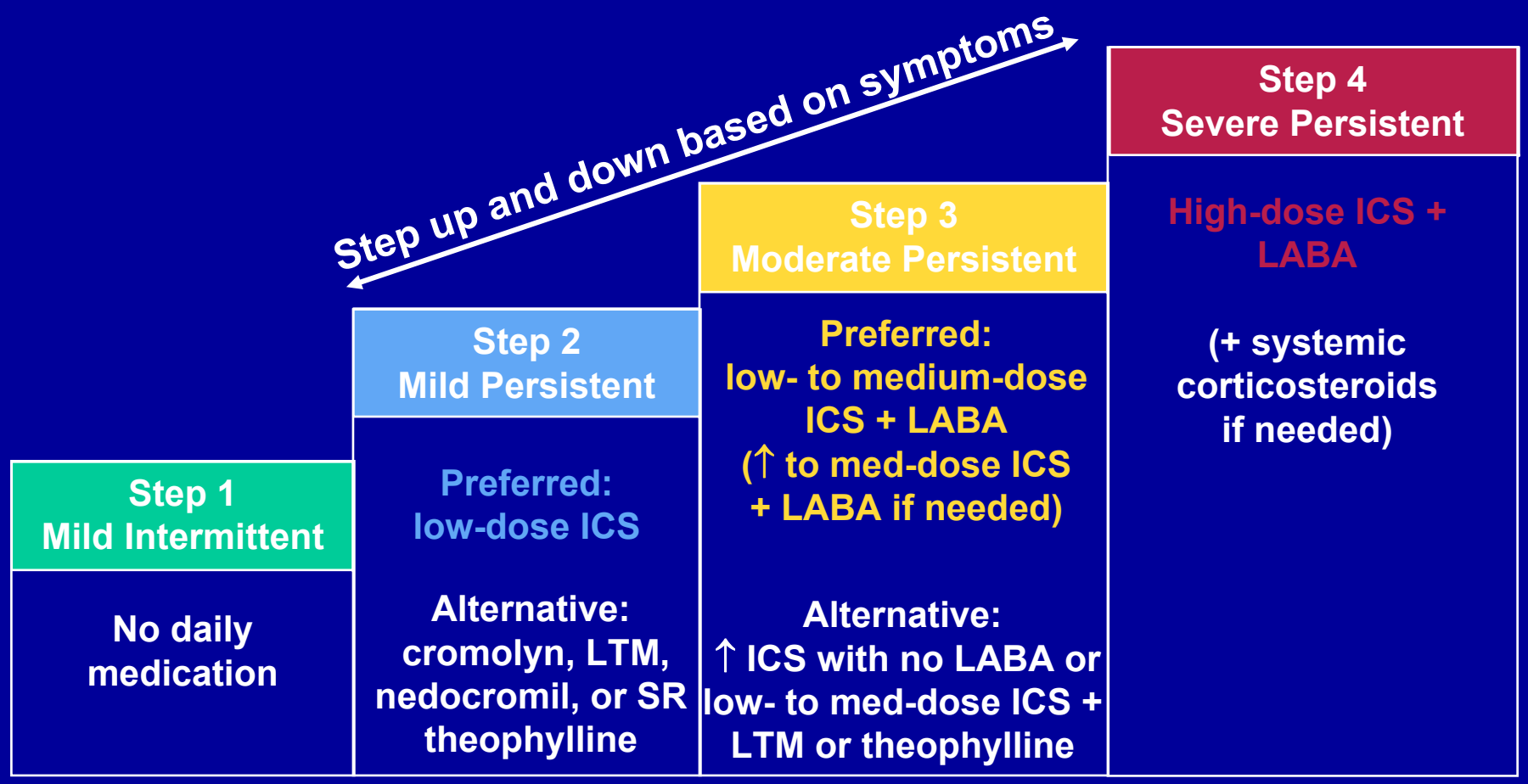
Stepwise Approach to Therapy for Children Aged ≤5 Years



ICS = inhaled corticosteroid; LABA = long-acting β_2-adrenergic agonist; LTRA = leukotriene receptor antagonist.

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

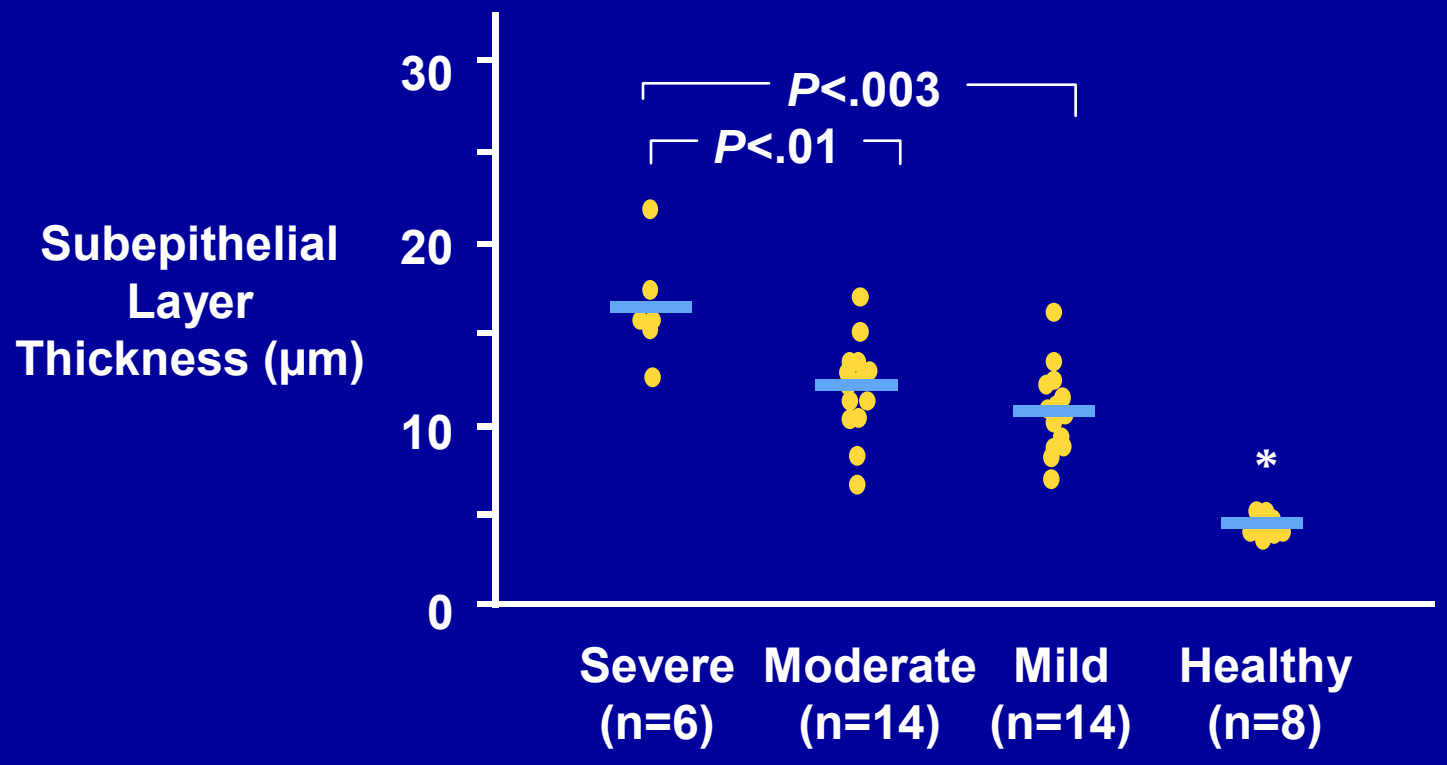
Stepwise Approach to Therapy for Adults and Children Aged >5 Years



ICS = inhaled corticosteroid; LABA = long-acting β_2-adrenergic agonist; LTM = leukotriene modifier; SR = sustained release.

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

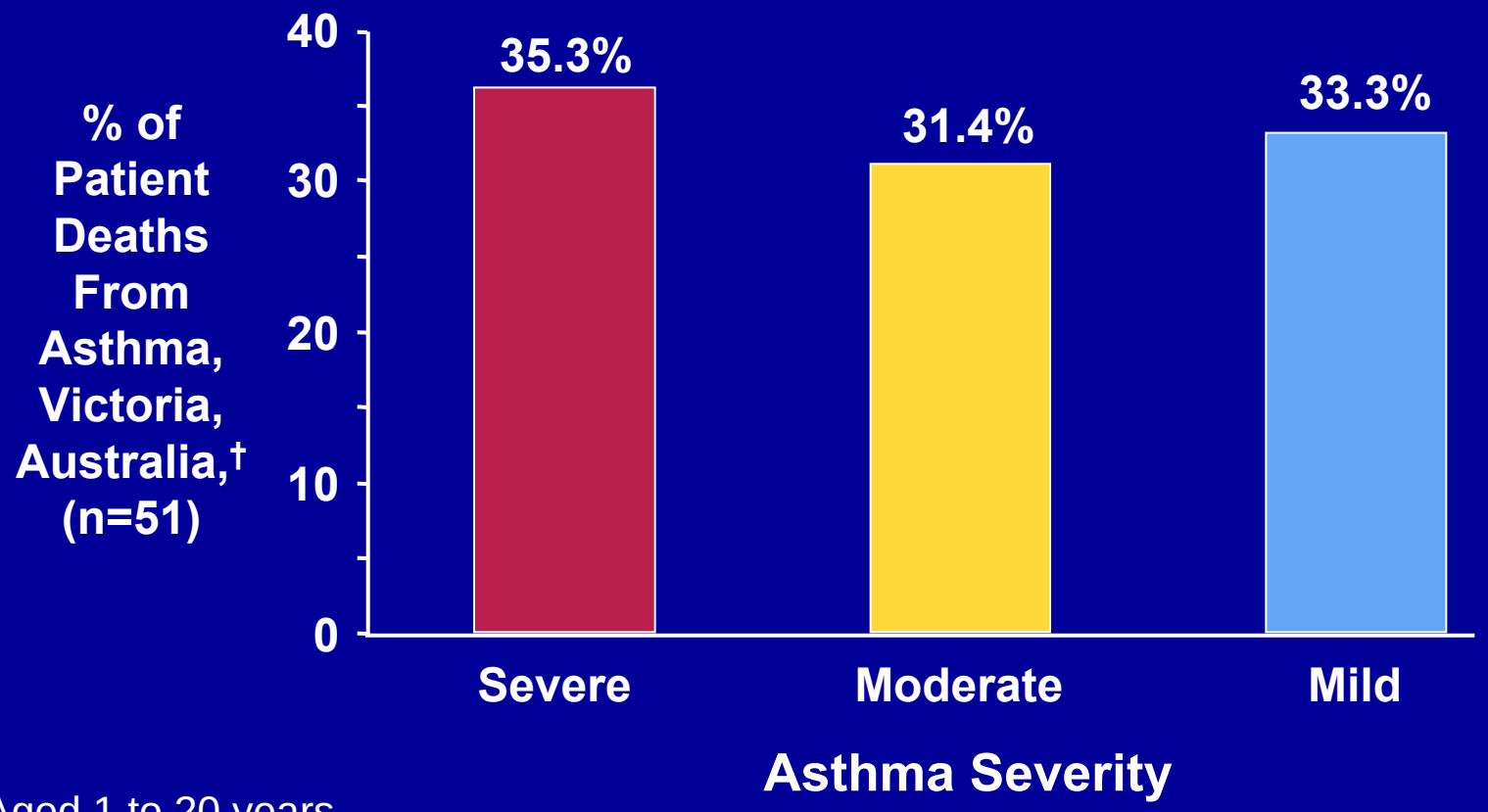
Airway Remodeling Occurs Even in Patients With Mild Asthma



*P<.001, healthy subjects vs patients with asthma.

Chetta et al. *Chest.* 1997;111:852-7.

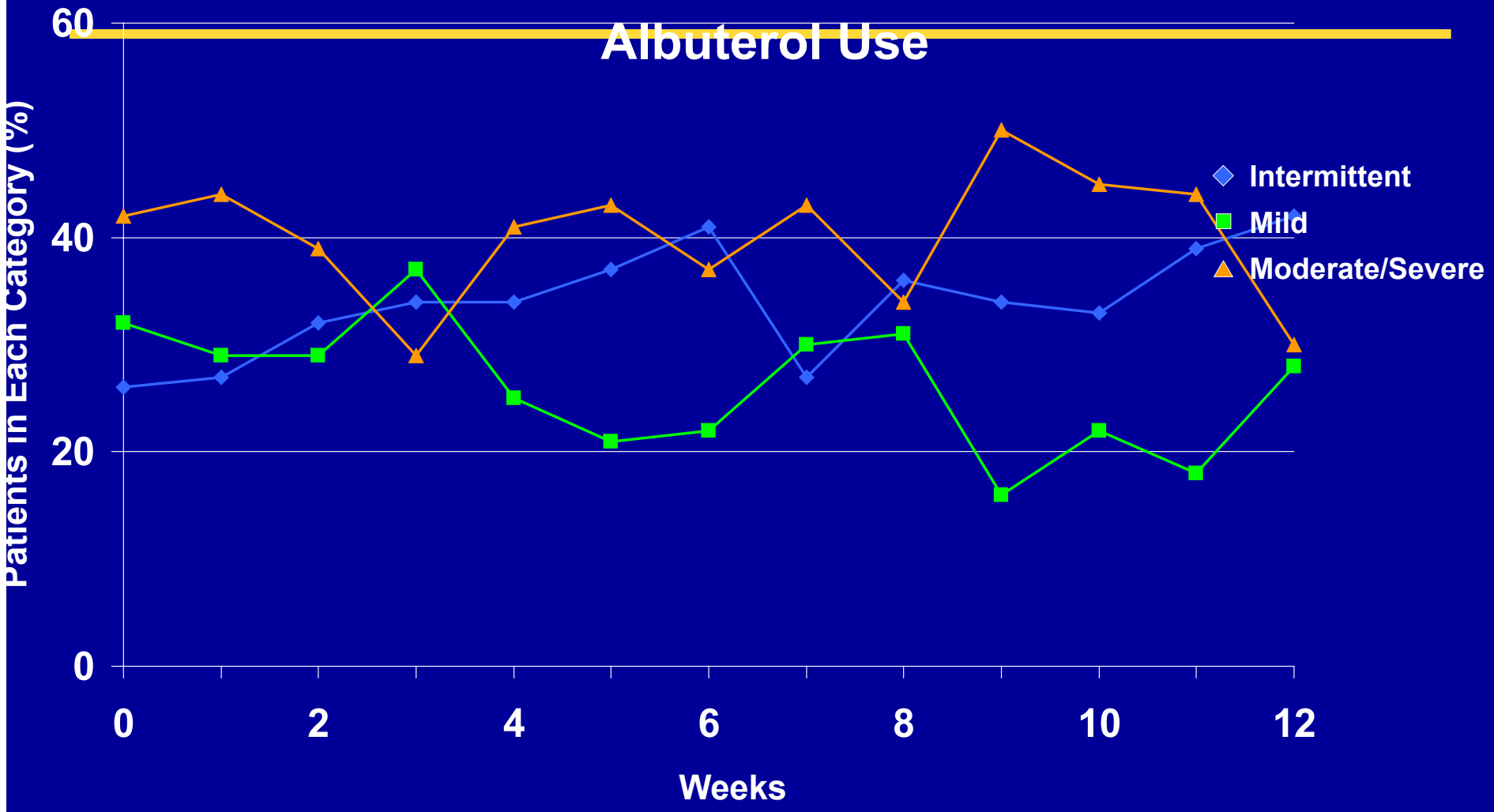
Pediatric* Asthma Deaths: Mild Disease Also Poses Risks



*Aged 1 to 20 years.
†Data were assessed retrospectively and based on interviews with families of the deceased, the certifying doctor, and other health professionals. Asthma severity classification was based on subjective judgment and consensus of the investigators.

Robertson et al. *Pediatr Pulmonol*. 1992;13:95-100.

Asthma Variability



Calhoun et al. *J Allergy Clin Immunol.* 2003;112:1088-1094.

Definition of Severity from GINA guidelines, 2002 (what we're used to)

- Severity classification
  - Mild Intermittent
  - Mild Persistent
  - Moderate Persistent
  - Severe Persistent

- based on combination of 3 categories:
  1) Medication (Step 1, 2, 3, 4)
  2) Symptom frequency
  3) Pulmonary function

GINA= Global Initiative for Asthma

NHLBI Assessment and Monitoring, now more complicated

- Baseline Severity
  - ~~Mild Intermittent~~
  - Mild Persistent
  - Moderate Persistent
  - Severe Persistent
- based on combination of multiple categories:

1) Medication ✓ **keep (Now: Step 1,2,3,4,5,6)→ infer severity level from least amount of medication to maintain control. Related to responsiveness to treatment. Differs by age 0-4y, 5-11y, ≥12y.**
2) Symptom frequency
3) Pulmonary function

} **A. "Impairment"**

B. Risk of adverse events (new)

Ongoing Control

NHLBI Same (more or less):

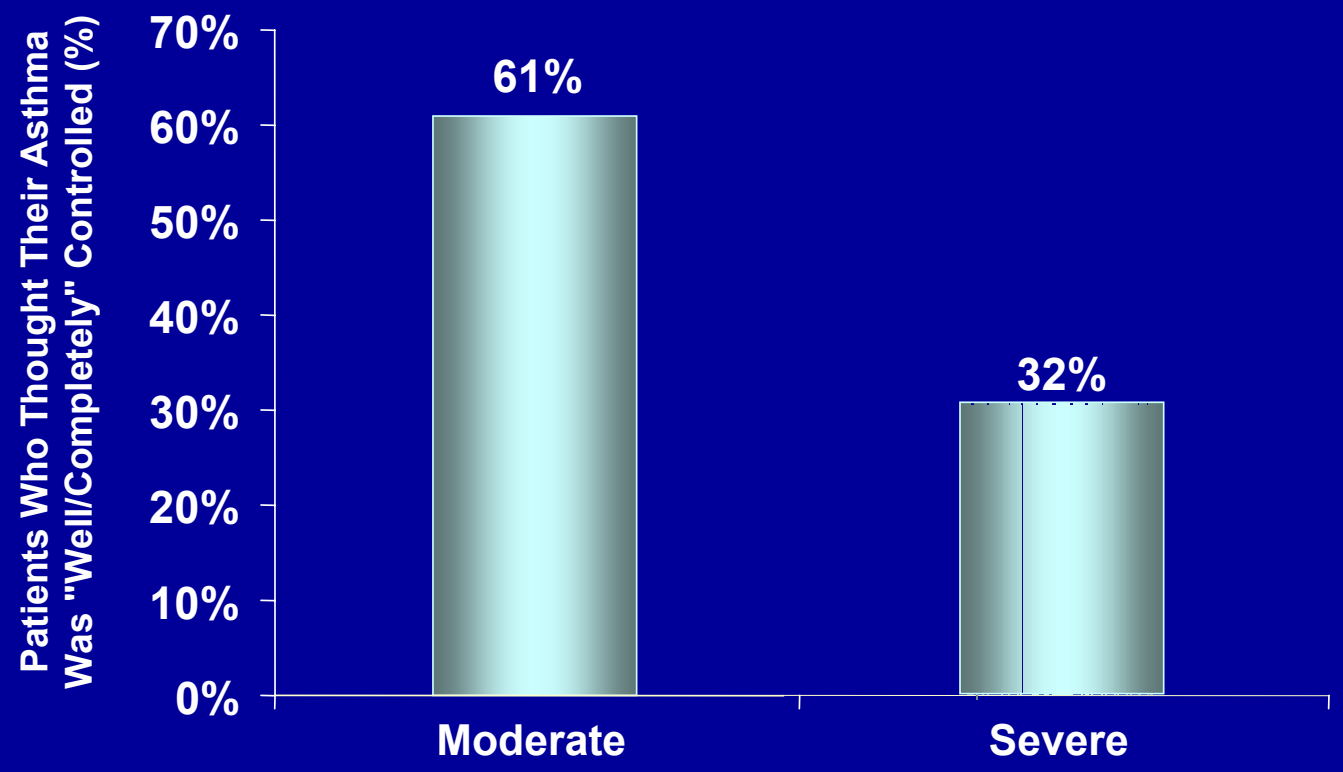
- Inflammation
- Airflow obstruction (at least partially reversible) or AHR present
- ICS, mainstay
- Safety, growth
- Self-monitoring is important
- PEF diary
- Action Plan
- Evaluate role of allergens, irritants.
- Allergen avoidance
- Treat co-morbidity
- Encourage physical activity
- Asthma self-management education needs repetition, reinforcement
- Active partnership
- Provider education

Assessment and Monitoring Definitions

- Severity: the intrinsic intensity of the disease process. Severity is measured most easily and directly in a patient not receiving long-term control therapy.
- Control: the degree to which the manifestations of asthma are minimized and the goals of therapy are met
- Responsiveness: the ease with which asthma control is achieved by therapy
- Impairment: frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced.
- Risk: the likelihood of either asthma exacerbations, progressive decline in lung function or risk of adverse effects from medication.
- Impairment and Risk may respond differentially to treatment.

How Can Asthma Control Be Measured?

Many Patients With Frequent Symptoms Consider Their Asthma "Well/Completely" Controlled



Moderate
- Daily daytime symptoms
- Nighttime symptoms >1 night/week

Severe
- Continual daytime symptoms
- Frequent nighttime symptoms

Asthma in America™. A Landmark Survey. Executive Summary. **SRBI. 1998.**

Results of a large, national telephone survey of 2,509 adults with asthma or parents of children with asthma.

Asthma Control Test™ (ACT) for Patients 12 Years and Older

						Score
1. In the past **4 weeks,** how much of the time did your **asthma** keep you from getting as much done at work, school or at home?	All of the time 1	Most of the time 2	Some of the time 3	A little of the time 4	None of the time 5	
	More than once a day 1	Once a day 2	3 to 6 times a week 3	Once or twice a week 4	Not at all 5	
	4 or more nights a week 1	2 or 3 nights a week 2	Once a week 3	Once or twice 4	Not at all 5	
	3 or more times per day 1	1 or 2 times per day 2	2 or 3 times per week 3	Once a week or less 4	Not at all 5	
	Not controlled at all 1	Poorly controlled 2	Somewhat controlled 3	Well controlled 4	Completely controlled 5	

Childhood Asthma Control Test

Questions Completed by Child

SCORE

1. How is your asthma today?

0	1	2	3
Very bad	Bad	Good	Very Good

2. How much of a problem is your asthma when you run, exercise or play sports?

0	1	2	3
It's a big problem, I can't do what I want to do.	It's a problem and I don't like it.	It's a little problem but it's okay.	It's not a problem

3. Do you cough because of your asthma?

0	1	2	3
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time

4. Do you wake up during the night because of your asthma?

0	1	2	3
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time

July 2006: Revised NHLBI Guidelines, per R. Lemanske 1-27-06

1) SEVERITY: Impairment and Risk: e.g. Mild Intermittent with High Risk.

	Mild Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
I. Impairment				
• PEF				
• FEV1				
• Symptoms				
• SABA				
• QOL				
II. Risk				
• Frequency and Severity of exacerbations	?? What levels: Mild, moderate, severe? Low, medium, high?			
• Loss of lung function over time				
• Side effects of medication				

2) CONTROL:

- Will add a measure separate from Severity.
- Control level for a certain Impairment.

"RULES OF TWO™"*

Patients Are Candidates for Maintenance Therapy If …

- Use a quick-relief inhaler **>2** times /week
- Awaken due to asthma **>2** times/month
- More than **2** times/year:
  - Refill a quick-relief inhaler
  - Receive a "burst" of oral steroid
  - Unscheduled acute asthma care

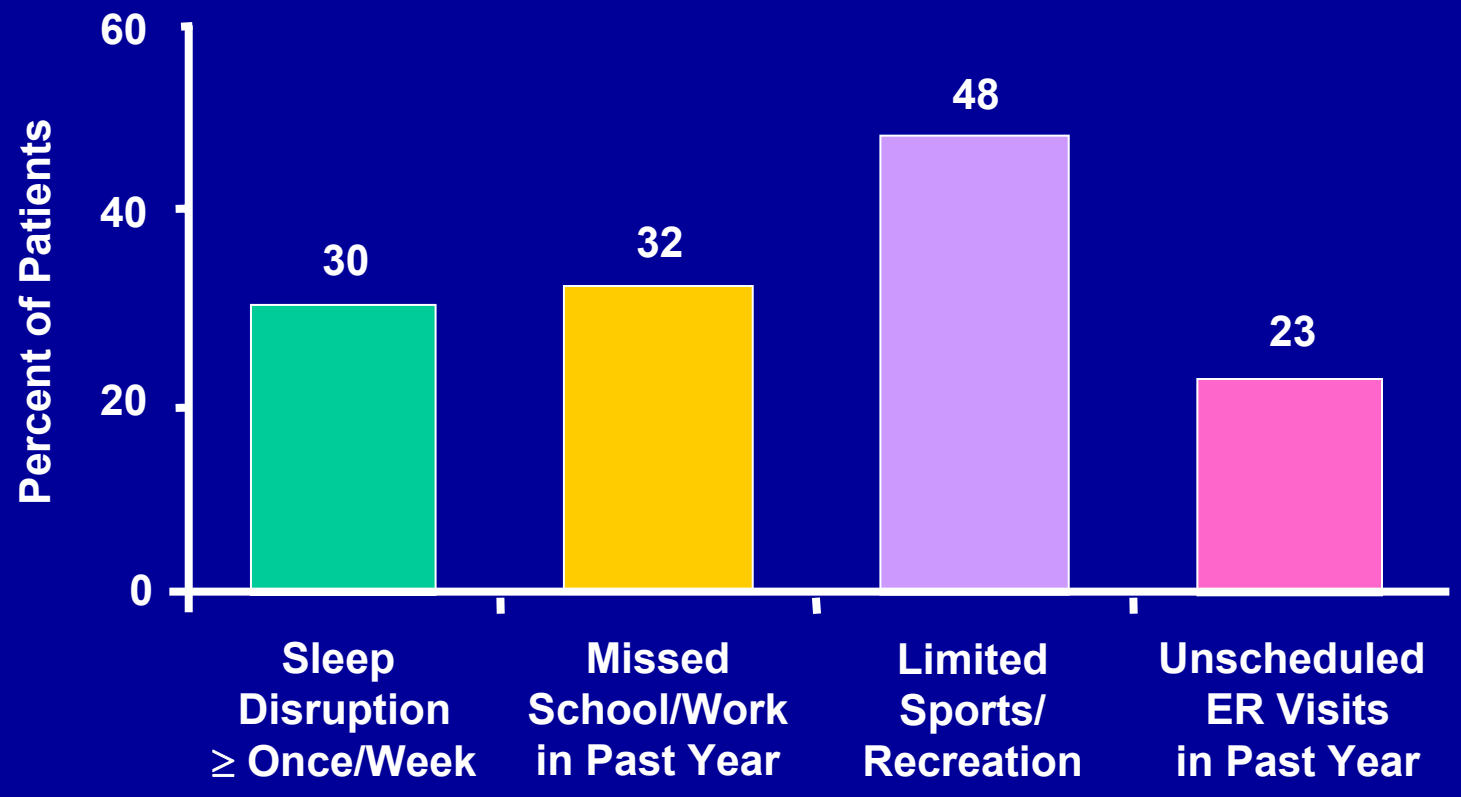
*"RULES OF TWO™" is a trademark of the Baylor Health Care System.

NIH Established Goals of Asthma Therapy

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no missed school/work
- Maintain (near) normal pulmonary function
- Minimal use of inhaled short-acting beta$_2$-agonists
- Minimal or no adverse effects from medications

Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. **NIH, NHLBI. May 2003 (reprint). NIH publication 02-5075.**

Many Patients Fail to Meet the Goals of Asthma Therapy

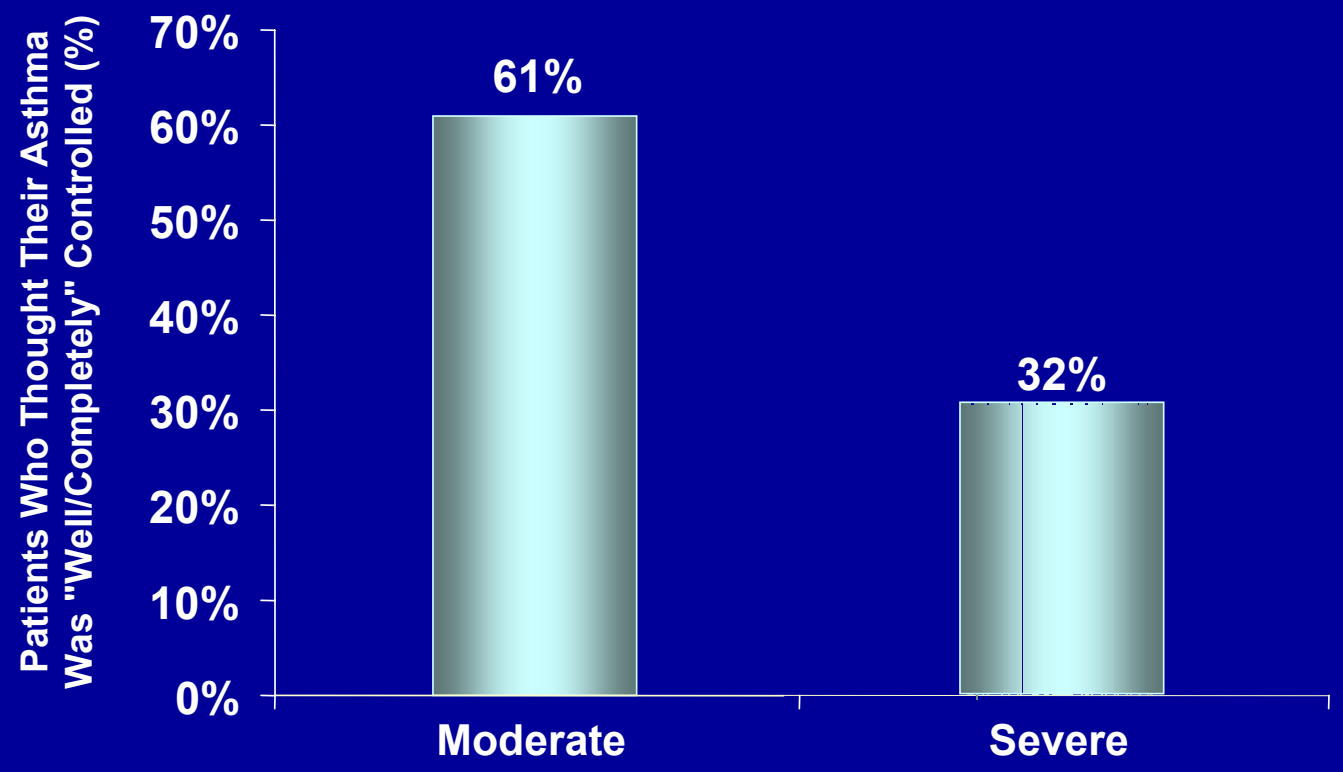


Base: All respondents (unweighted *n*=2509)

***Asthma in America™. A Landmark Survey. Executive Summary.* SRBI. 1998.**

Results of a large, national telephone survey of 2,509 adults with asthma or parents of children with asthma.

Many Patients With Frequent Symptoms Consider Their Asthma "Well/Completely" Controlled



Moderate
- Daily daytime symptoms
- Nighttime symptoms >1 night/week

Severe
- Continual daytime symptoms
- Frequent nighttime symptoms

Asthma in America™. A Landmark Survey. Executive Summary. **SRBI. 1998.**

Results of a large, national telephone survey of 2,509 adults with asthma or parents of children with asthma.

Assessing Asthma Control
A Need for New Tools

- Many children with asthma experience frequent symptoms and activity limitations
- Comprehensive assessment of disease control is needed, including:
  - Symptoms, activity level, albuterol use
  - Objective measures: spirometry, PEFR
- Multiple approaches can be utilized to assess asthma control
- The NIH goals of therapy should be considered in determining control

Asthma Control Test™ (ACT) for Patients 12 Years and Older

						Score
1. In the past **4 weeks,** how much of the time did your **asthma** keep you from getting as much done at work, school or at home?	All of the time 1	Most of the time 2	Some of the time 3	A little of the time 4	None of the time 5	
	More than once a day 1	Once a day 2	3 to 6 times a week 3	Once or twice a week 4	Not at all 5	
	4 or more nights a week 1	2 or 3 nights a week 2	Once a week 3	Once or twice 4	Not at all 5	
	3 or more times per day 1	1 or 2 times per day 2	2 or 3 times per week 3	Once a week or less 4	Not at all 5	
	Not controlled at all 1	Poorly controlled 2	Somewhat controlled 3	Well controlled 4	Completely controlled 5	

Childhood Asthma Control Test

Questions Completed by Child

SCORE

1. How is your asthma today?

0	1	2	3
Very bad	Bad	Good	Very Good

2. How much of a problem is your asthma when you run, exercise or play sports?

0	1	2	3
It's a big problem, I can't do what I want to do.	It's a problem and I don't like it.	It's a little problem but it's okay.	It's not a problem

3. Do you cough because of your asthma?

0	1	2	3
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time

4. Do you wake up during the night because of your asthma?

0	1	2	3
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time

What to Do If the ACT Score Is ≤19

- Obtain an appropriate medical history
  - Consider recent symptoms, activity limitation, peak flow measurements, current medications including albuterol use, adherence with medication, exposure to asthma triggers, etc.
- Perform an appropriate clinical examination
- Perform lung function assessment, if clinically indicated
- Establish asthma management plan and follow-up, including repeating ACT at next visit

ASTHMA 2007

- Asthma Facts
- Guidelines Preview
- Severity v. Control
- Discussion

Education for Partnership in Asthma Care (Component 3)

- There are many potential points of care and sites available for self-management outside the office setting (e.g. clinics, medical offices, EDs and hospitals, pharmacies, homes, community sites, schools).
- "Action Plan" = both daily management and early recognition of actions for exacerbation (one term).
- Reviewed system-based interventions to improve quality of asthma care, to support clinical decision-making and to enhance clinical information systems.
- Reviewed tested programs for education, multidimensional, interactive, and practice-based studies.

OLINAVY
Harry Potter
PROVIDENCE

NOT THE END & THANKS

MEDICATIONS

- Inhaled Corticosteroids (ICS)
- Long-acting Inhaled Beta $_2$ –Agonists (LABA)
- Combined Medications
- Cromolyn and Nedocromil
- Leukotrienes Modifiers
  - Montelukast
  - Zileutin
- Methylxanthines
- Immunoregulation
  - Allergy Shots
  - Xolair

MANAGEMENT

- “Whole”istic care
- Evaluation, environmental controls, trigger identification, education, action plans etc.
- Medications
- Immunotherapy
- Advanced & newer therapies

Estimated Comparative Daily Dosages for Inhaled Corticosteroids

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Adult	Child*	Adult	Child*	Adult	Child*
Beclomethasone CFC 42 or 84 mcg/puff	168–504 mcg	84–336 mcg	504–840 mcg	336–672 mcg	> 840 mcg	> 672 mcg
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	80–160 mcg	240–480 mcg	160–320 mcg	> 480 mcg	> 320 mcg
Budesonide DPI 200 mcg/inhalation	200–600 mcg	200–400 mcg	600–1,200 mcg	400–800 mcg	> 1,200 mcg	> 800 mcg
Inhalation suspension for nebulization (child dose)		0.5 mg		1.0 mg		2.0 mg
Flunisolide 250 mcg/puff	500–1,000 mcg	500–750 mcg	1,000–2,000 mcg	1,000–1,250 mcg	> 2,000 mcg	> 1,250 mcg
Fluticasone MDI: 44, 110, or 220 mcg/puff	88–264 mcg	88–176 mcg	264–660 mcg	176–440 mcg	> 660 mcg	> 440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	100–200 mcg	300–600 mcg	200–400 mcg	> 600 mcg	> 400 mcg
Triamcinolone acetonide 100 mcg/puff	400–1,000 mcg	400–800 mcg	1,000–2,000 mcg	800–1,200 mcg	> 2,000 mcg	> 1,200 mcg

* Children ≤ 12 years of age

Usual Dosages for Long-Term-Control Medications

Medication	Dosage Form	Adult Dose	Child Dose*
Inhaled Corticosteroids *(See Estimated Comparative Daily Dosages for Inhaled Corticosteroids.)*			
Systemic Corticosteroids		*(Applies to all three corticosteroids.)*	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	■ 7.5–60 mg daily in a single dose in a.m. or qod as needed for control	■ 0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	■ Short-course "burst" to achieve control: 40–60 mg per day as single or 2 divided doses for 3–10 days	■ Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		
Long-Acting Inhaled Beta$_2$-Agonists *(Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids.)*			
Salmeterol	MDI 21 mcg/puff	2 puffs q 12 hours	1–2 puffs q 12 hours
	DPI 50 mcg/blister	1 blister q 12 hours	1 blister q 12 hours
Formoterol	DPI 12 mcg/single-use capsule	1 capsule q 12 hours	1 capsule q 12 hours
Combined Medication			
Fluticasone/Salmeterol	DPI 100, 250, or 500 mcg/50 mcg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma
Cromolyn and Nedocromil			
Cromolyn	MDI 1 mg/puff	2–4 puffs tid-qid	1–2 puffs tid-qid
	Nebulizer 20 mg/ampule	1 ampule tid-qid	1 ampule tid-qid
Nedocromil	MDI 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid
Leukotriene Modifiers			
Montelukast	4 or 5 mg chewable tablet	10 mg qhs	4 mg qhs (2–5 yrs)
	10 mg tablet		5 mg qhs (6–14 yrs)
			10 mg qhs (> 14 yrs)
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	20 mg daily (7–11 yrs) (10 mg tablet bid)
Zileuton	300 or 600 mg tablet	2,400 mg daily (give tablets qid)	
Methylxanthines *(Serum monitoring is important [serum concentration of 5–15 mcg/mL at steady state]).*			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: ■ < 1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥ 1 year of age: 16 mg/kg/day

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3–10)

Medication	Dosages		
	Adult Dose	Child Dose*	Comments
Short-Acting Inhaled Beta$_2$-Agonists			
Albuterol			
Nebulizer solution (5.0 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization	Only selective beta$_2$-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min.
MDI (90 mcg/puff)	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver. Use spacer/holding chamber	As effective as nebulized therapy if patient is able to coordinate.
Bitolterol			
Nebulizer solution (2 mg/mL)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 mcg/puff)	See albuterol dose	See albuterol dose	Has not been studied in severe asthma exacerbations.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3–10)

Medication	Dosages		
	Adult Dose	Child Dose*	Comments
Levalbuterol (R-albuterol)			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL)	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed, or 5–7.5 mg/hour continuously	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed, or 0.25 mg/kg/hour by continuous nebulization	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects.
Pirbuterol			
MDI (200 mcg/puff)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations.
Systemic (Injected) Beta$_2$-Agonists			
Epinephrine 1:1000 (1 mg/mL)	0.3–0.5 mg every 20 minutes for 3 doses sq	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.25 mg every 20 minutes for 3 doses sq	0.01 mg/kg every 20 minutes for 3 doses then every 2–6 hours as needed sq	No proven advantage of systemic therapy over aerosol.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3–10)

Medication	Dosages		
	Adult Dose	Child Dose*	Comments
Anticholinergics			
Ipratropium bromide			
Nebulizer solution (0.25 mg/mL)	0.5 mg every 30 minutes for 3 doses then every 2–4 hours as needed	0.25 mg every 20 minutes for 3 doses, then every 2 to 4 hours	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to beta$_2$-agonist therapy.
MDI (18 mcg/puff)	4–8 puffs as needed	4–8 puffs as needed	Dose delivered from MDI is low and has not been studied in asthma exacerbations.
Ipratropium with albuterol			
Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	3 mL every 30 minutes for 3 doses, then every 2–4 hours as needed	1.5 mL every 20 minutes for 3 doses, then every 2–4 hours	Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	4–8 puffs as needed	4–8 puffs as needed	

Usual Dosages for Long-Term-Control Medications

Medication	Dosage Form	Adult Dose	Child Dose*
Inhaled Corticosteroids *(See Estimated Comparative Daily Dosages for Inhaled Corticosteroids.)*			
Systemic Corticosteroids		*(Applies to all three corticosteroids.)*	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	■ 7.5–60 mg daily in a single dose in a.m. or qod as needed for control	■ 0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	■ Short-course "burst" to achieve control: 40–60 mg per day as single or 2 divided doses for 3–10 days	■ Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		
Long-Acting Inhaled Beta$_2$-Agonists *(Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids.)*			
Salmeterol	MDI 21 mcg/puff	2 puffs q 12 hours	1–2 puffs q 12 hours
	DPI 50 mcg/blister	1 blister q 12 hours	1 blister q 12 hours
Formoterol	DPI 12 mcg/single-use capsule	1 capsule q 12 hours	1 capsule q 12 hours
Combined Medication			
Fluticasone/Salmeterol	DPI 100, 250, or 500 mcg/50 mcg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma
Cromolyn and Nedocromil			
Cromolyn	MDI 1 mg/puff	2–4 puffs tid-qid	1–2 puffs tid-qid
	Nebulizer 20 mg/ampule	1 ampule tid-qid	1 ampule tid-qid
Nedocromil	MDI 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid
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	10 mg tablet		5 mg qhs (6–14 yrs)
			10 mg qhs (> 14 yrs)
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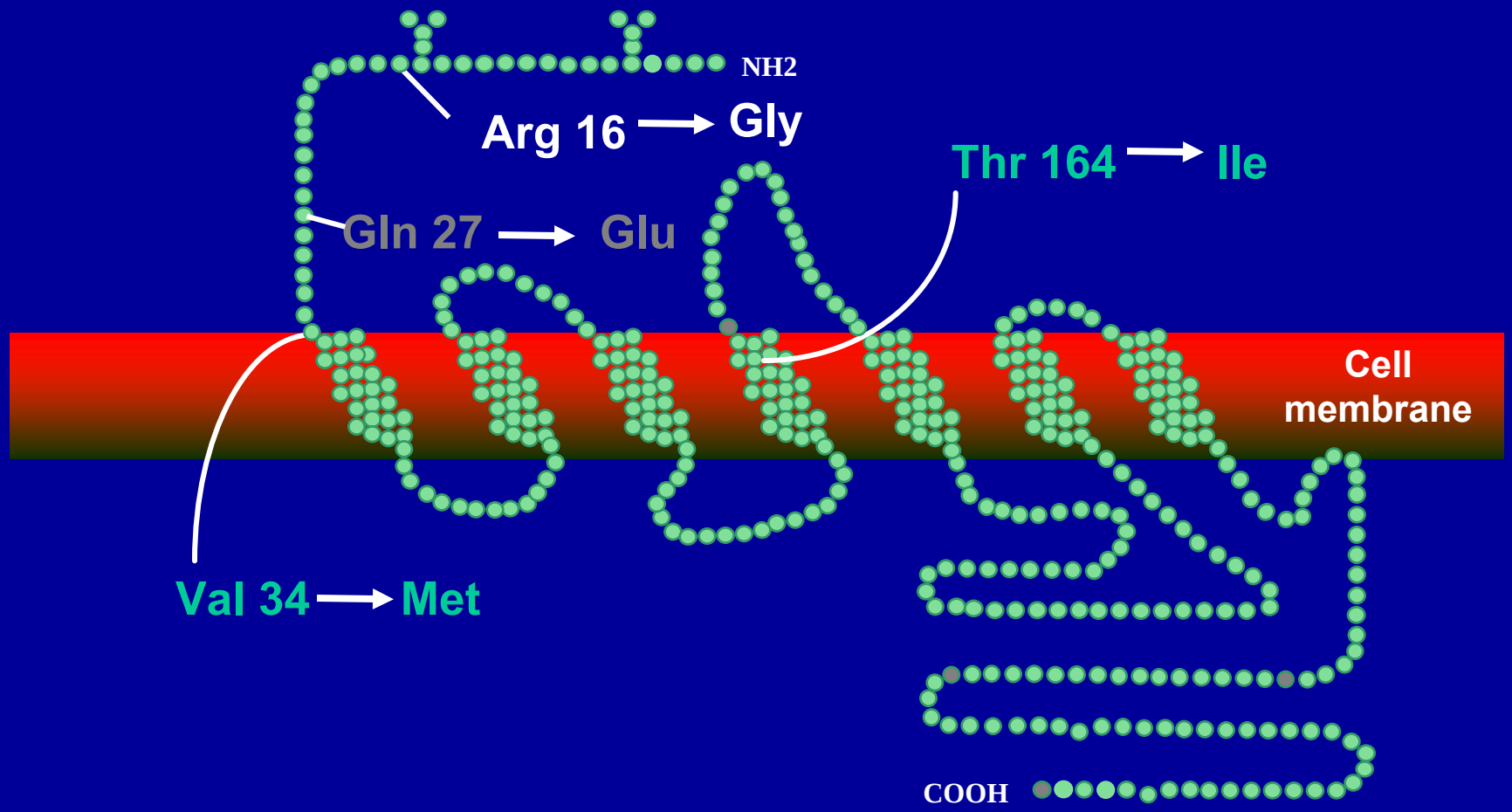
Zileuton	300 or 600 mg tablet	2,400 mg daily (give tablets qid)	
Methylxanthines *(Serum monitoring is important [serum concentration of 5–15 mcg/mL at steady state]).*			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: ■ < 1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥ 1 year of age: 16 mg/kg/day

ASTHMA 2006

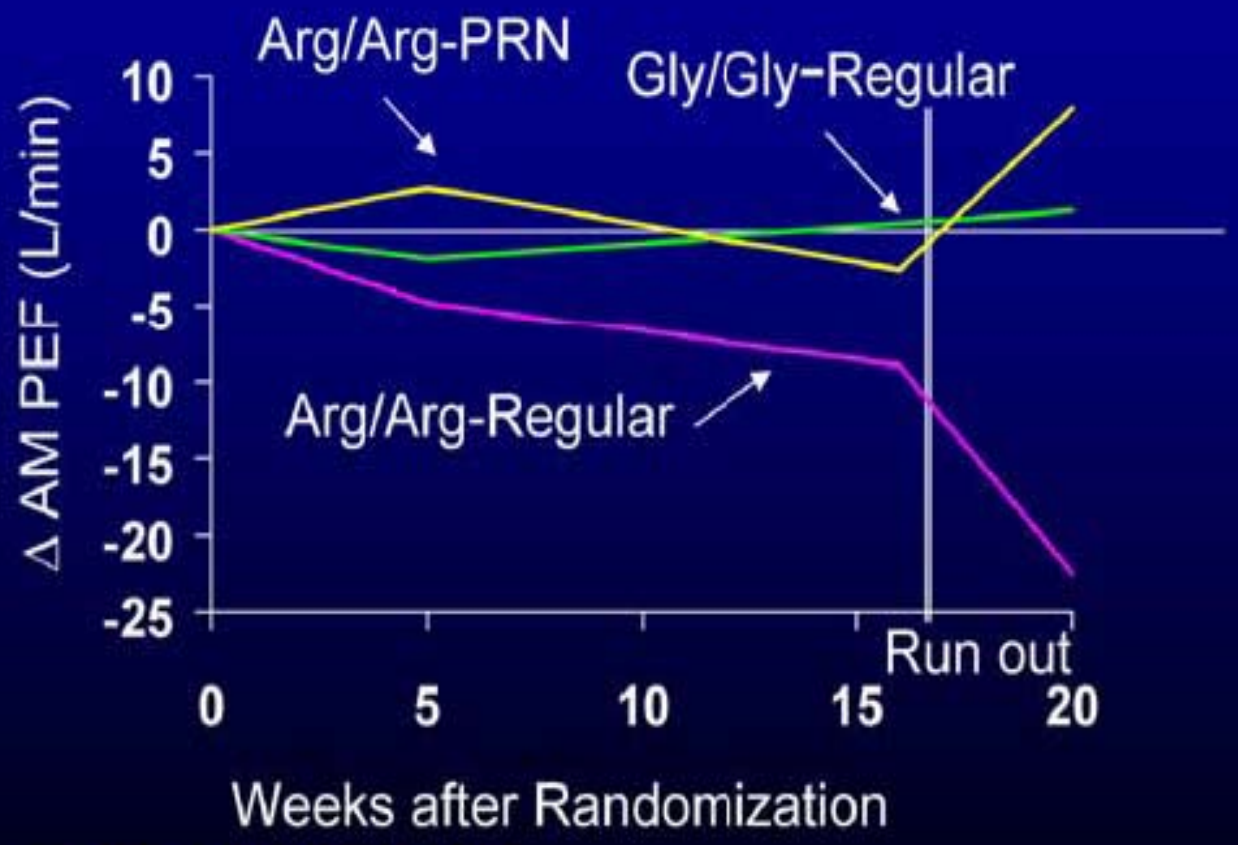
- Asthma Facts
- Bronchiolitis to Asthma to COPD ?
- Guidelines with preview
- New Issues?

β_2-Adrenergic Receptor Polymorphisms



Reihsaus et al. *Am J Respir Cell Mol Biol.* 1993;8:334-339

BAGS Study of β-2 receptor polymorphisms in asthma



Israel E & the ACRN, AJRCCM; 2000

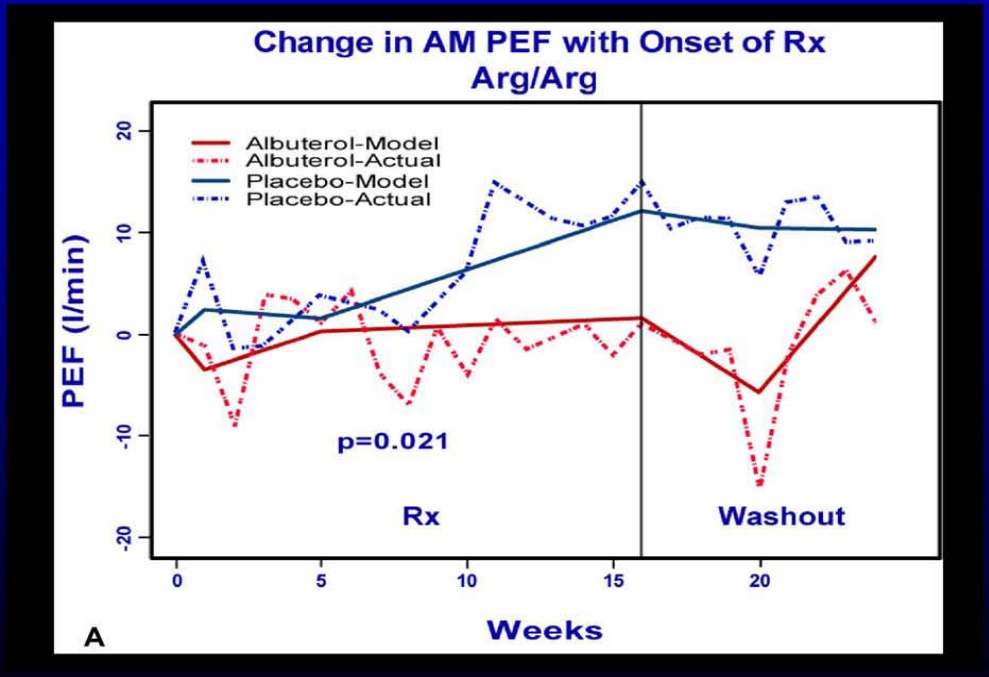
BARGE Protocol Overview

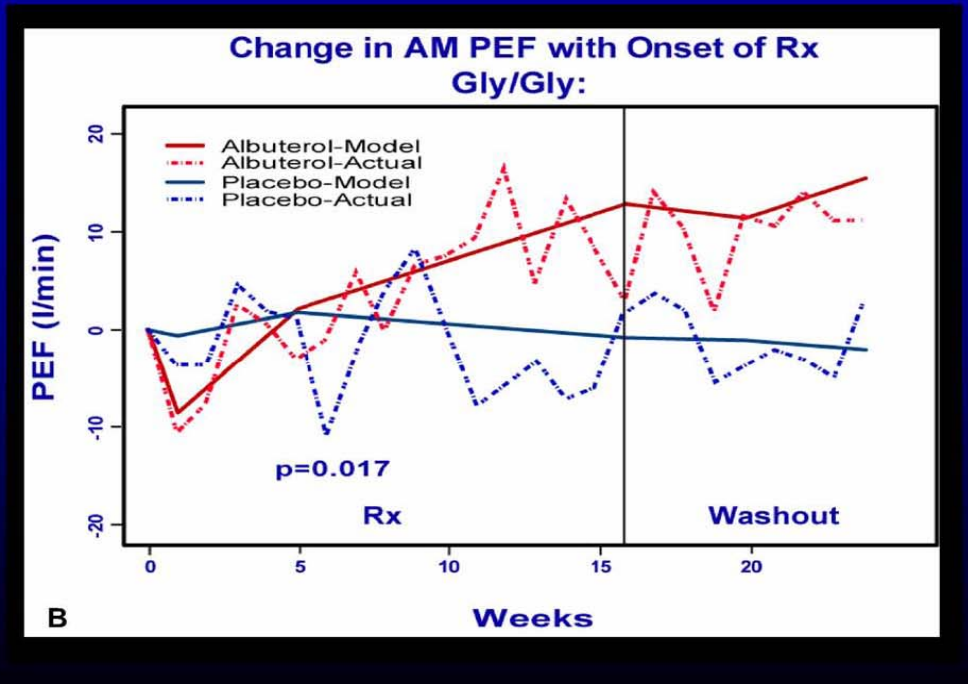
- Prospective randomized, placebo-controlled, double-blind trial of regular vs. minimal albuterol in each genotype
- To minimize B-agonist use patients were provided ipratropium bromide (IB) for rescue use and instructed only to use albuterol if sx were not relieved by IB

Israel et al. *Lancet.* 2004; 364:1505-1512

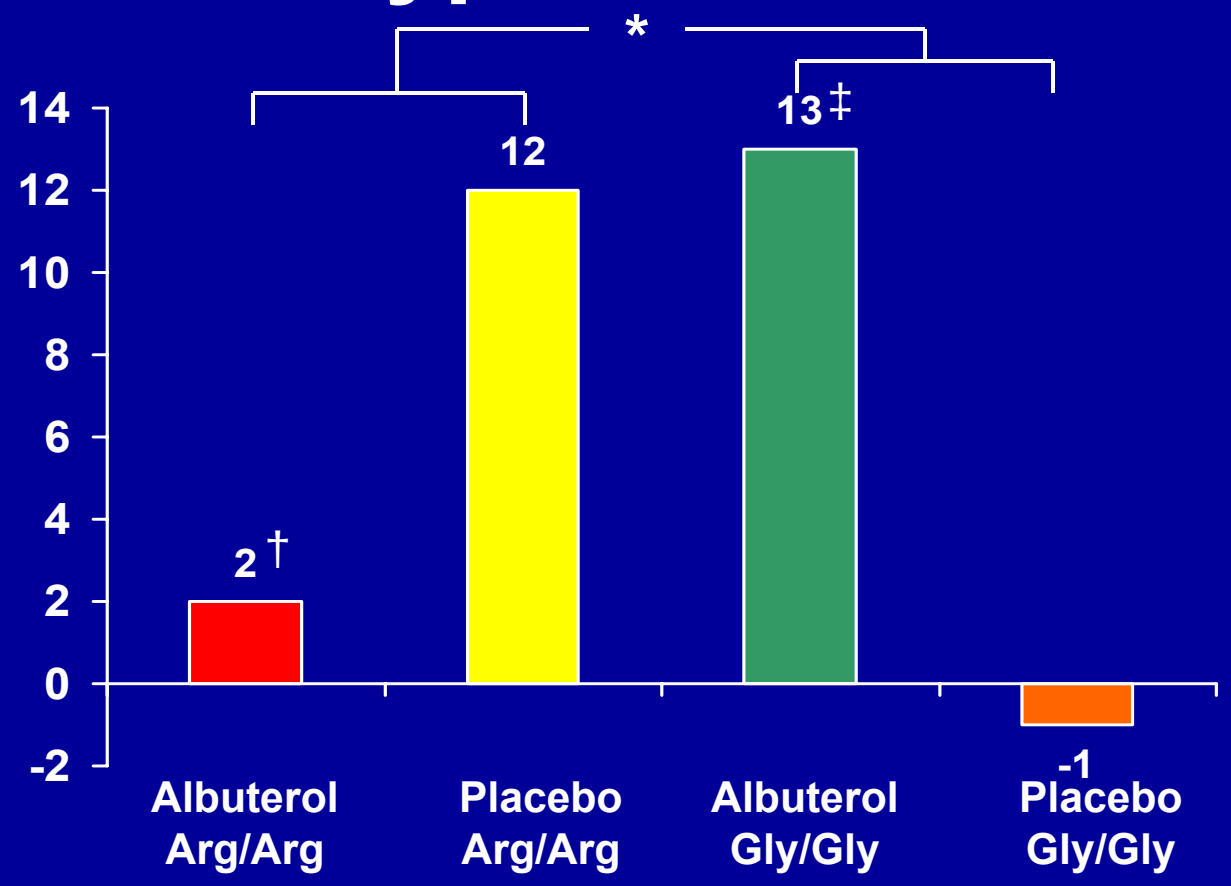
Regularly scheduled albuterol treatment in asthma: β-2 adrenergic receptor polymorphisms In asthma.

Israel E, Lancet 2004.





Mean Change in AM PEF by Genotype at Week 16



* Mean Arg/Arg minus Gly/Gly treatment difference= -24 (-37 to -12), *P*=0.0003.
† *P*=0.0209 vs Placebo Arg/Arg.
‡ *P*=0.0175 vs Placebo Gly/Gly.

Israel E, et al. *Lancet.* 2004;364:1505-1512

Conclusions

- The prospective, genotype stratified trial demonstrates that the genotype at the beta$_2$-adrenergic receptor influences the response to albuterol treatment
- Asthmatics with the Arg/Arg genotype (~1/6 of US asthmatics) may have improved asthma control when treated with minimal albuterol

Israel E, et al. *Lancet.* 2004;364:1505-1512

Racial Distributions of Haplotypes Containing Arg/Arg Polymorphisms

Haplotype#	Caucasions	Afr-Amer	Hisp	Asians
1	0.7	25.0	12.5	10.0
4	33.0	29.7	45.0	40.0
9	0.0	4.7	0.0	0.0

Drysdale: PNAS 2000, 97:10483-8)

PRO JO 6/2006

The Providence Journal NATION

Asthma drugs pose health risk, studies say

The increased incidents of hospitalization and death from such popular bronchodilators as Advair and Serevent raise the possibility that they may be taken off the market.

THE WASHINGTON POST

WASHINGTON — Popular and long-acting asthma medicines such as Advair and Serevent pose a substantially increased risk of hospitalization and death to users compared with placebos, according to a new analysis of 19 studies on the subject.

The analysis also found that the increased risks of the long-acting bronchodilators affect a broad range of users — more than doubling the rate at which asthma patients had to be hospitalized. Most experts have believed that the powerful bronchodilators are harmful only to a small number of people genetically predisposed to having a negative reaction.

"What we have here is a drug that increases the number of people who will die from the disease it is treating," said lead author Shelley Salpeter of Stanford University. "The long-acting bronchodilators can help reduce symptoms for many people, but we think the price in terms of serious side effects and deaths is unacceptable."

The Food and Drug Administration has voiced concerns about the widely used medicines, and last fall it required drug makers to prepare stiff new warnings to the package label. But the new analysis, published in the journal Annals of Internal Medicine, raises the possibility that the drug should be taken off the market if it continues to be so widely used.

1. Salpeter, Meta-analysis, Ann Int Med 2006
2. Nelson, SMART, Chest 2006

Meta-Analysis: Effect of LABAs on Severe Asthma Exacerbations and Asthma-related Deaths

- Randomized placebo-controlled lasting 3 mo.
- Pooled results of 19 trials with 33,826 subjects
- SMART study represents 26,000 subjects
- "The OR for deaths in this analysis was obtained solely from SMART."
- Interview Washington Post 6/6/06 "More than 3.5 million patients use the drug. In the new analysis, the authors estimated that Avair may be responsible for as many as 4000 asthma-related deaths per year."
- Author suggested in interview:
  - "stopping" the drug if asthma an exacerbation occurs
  - results raise possibility that Advair should be taken off the market

Salpeter, Shelley et. al. Ann Intern Med 2006

Number of Asthma Deaths* In US, 1979-2003

*1979 -1998 rates reflect the International Classification of Disease, 9th Revision Code 493. 1999 -2003 rates reflect the ICD 10th Revision Codes.

1. American Lung Association Epidemiology & Statistics Unit Research And Scientific Affairs. *Trends in Asthma Morbidity and Mortality*. May 2005. Available at: www.lungusa.org. Accessed June 14, 2006.
2. National Vital Statistics Report. *Deaths: Final Data for 2003*. April 2006. Available at: www.cdc.gov. Accessed June 14, 2006.

SMART

Salmeterol Multicenter Asthma Research Trial

- No inhaled long-acting beta$_2$-agonist
- $\geq$ 12 years of age

R

Salmeterol MDI 42mcg BID + Usual Care

(n=13,176)

week treatment period
Phone contact every 4 weeks

Placebo MDI BID + Usual Care

(n=13,179)

Clinic Visit

28 week supply of study medication provided

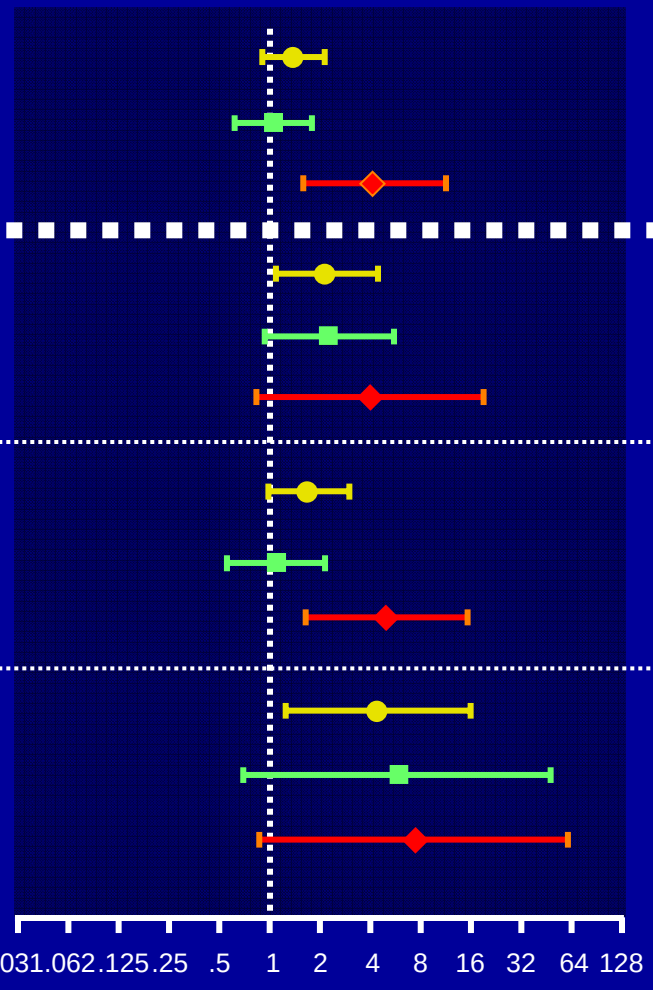
Nelson et al. *CHEST*. 2006;129:15-26

SMART Study Endpoints

- Primary Endpoint
  - Combined respiratory-related deaths or life-threatening experiences (intubation and ventilation)
  - Target sample size increased from 30,000 to 60,000 patients
- Key Secondary Endpoints
  - Respiratory-related deaths
  - Combined asthma-related deaths or life-threatening experiences
  - Asthma-related deaths

Nelson et al. *CHEST.* 2006; 129:15-26

SMART Results All Patients and Ethnic Subgroups



1° Endpoint	RR (95% CI)	SAL n	PLA n
Respiratory Death or Life Threatening Experience	1.40 (0.91, 2.14)	50	36
	1.05 (0.62, 1.76)	29	28
	4.10 (1.54, 10.90)	20	5
2° Endpoints			
Respiratory Death	2.16 (1.06, 4.41)	24	11
	2.29 (0.94, 5.56)	16	7
	3.88 (0.83, 18.26)	8	2
Asthma Death or Life Threatening Experience	1.71 (1.01, 2.89)	37	22
	1.08 (0.55, 2.14)	17	16
	4.92 (1.68,14.45)	19	4
Asthma Death	4.37 (1.25, 15.34)	13	3
	5.82 (0.70, 48.37)	6	1
	7.26 (0.89, 58.94)	7	1

● Total	N=13176	N=13179
■ Caucasian	N=9281	N=9361
◆ African American	N=2366	N=2319

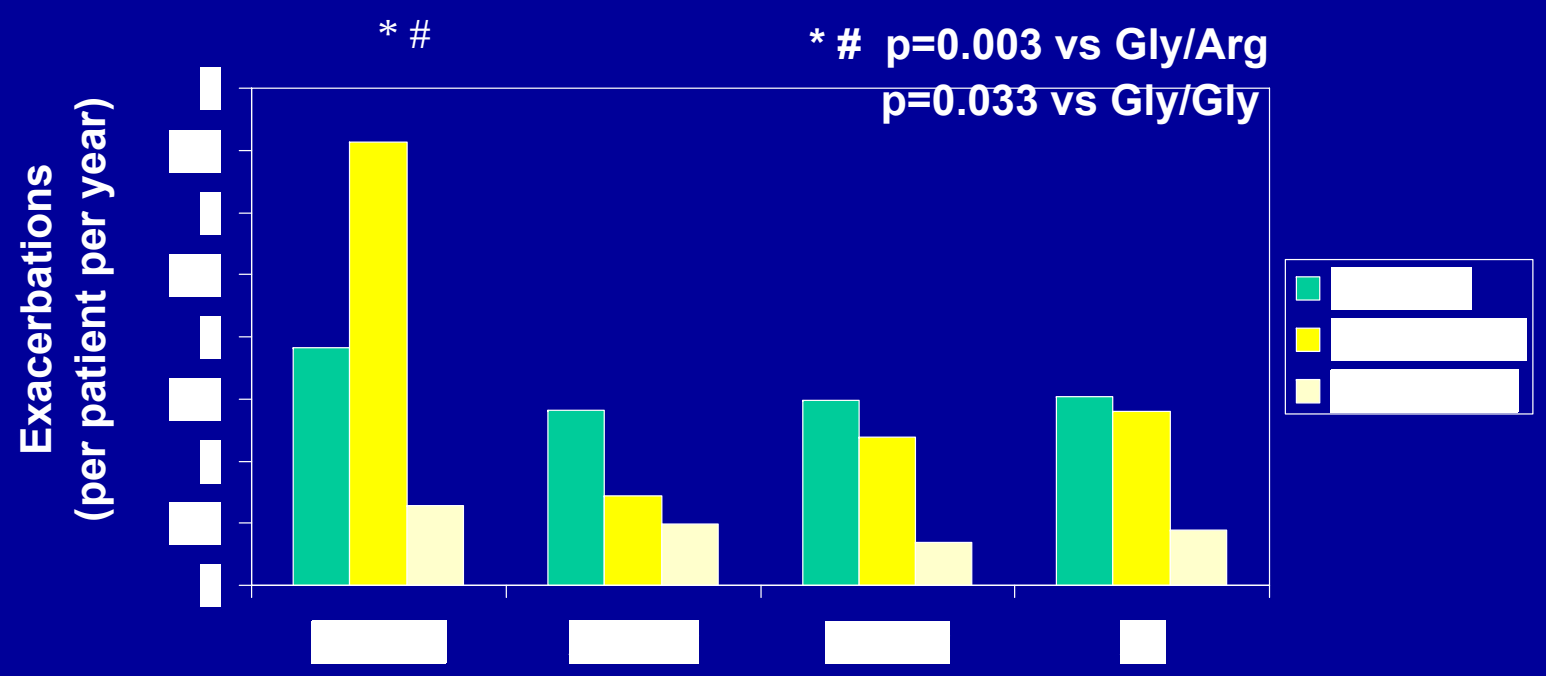
Nelson et al. *CHEST.* 2006; 129:15-26

MEDICATIONS

- Inhaled Corticosteroids (ICS)
- Long-acting Inhaled Beta $_2$ –Agonists (LABA)
- Combined Medications
- Cromolyn and Nedocromil
- Leukotrienes Modifiers
  - Montelukast
  - Zileutin
- Methylxanthines
- Immunoregulation
  - Allergy Shots
  - Xolair

Which Daily Controller Medication Do We Choose?

The Influence of β_2-Adrenergic Receptor Polymorphisms on Asthma Exacerbations



Taylor DR et al. *Thorax* . 2000;55: 762-767

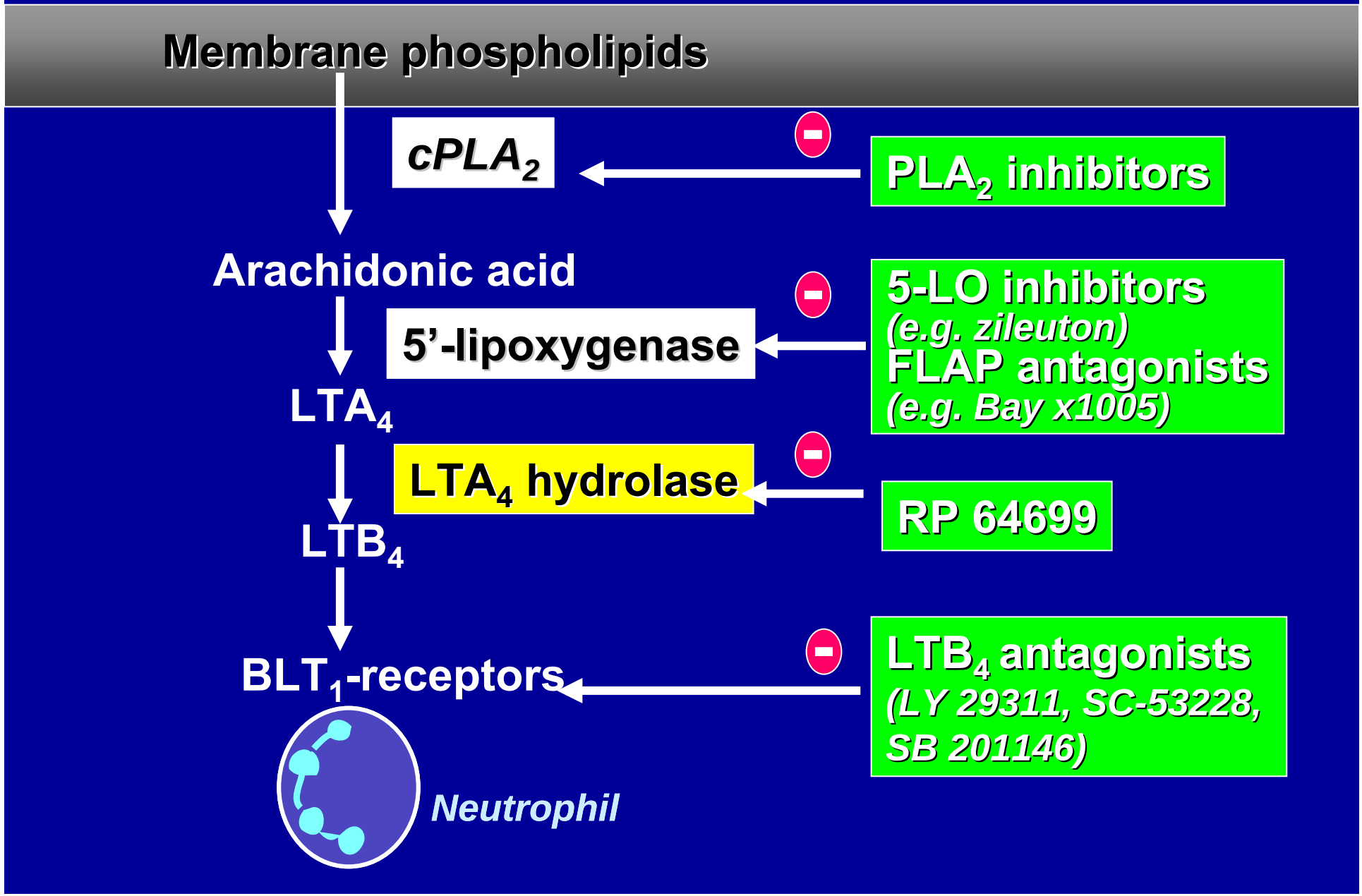
5'-LO INHIBITORS FOR AIRWAY DISEASE

↓ Cys-LTs: asthma (esp aspirin-sensitive asthma?)
not relevant in COPD
weakly effective

↓ LTB_4: neutrophil chemotaxis (BLT_1)
severe asthma
asthma exacerbations
stable COPD
COPD exacerbations

5'-oxo-ETE: chemoattraction of eosinophils, neutrophils,
OXE receptor: eos>neutc>monos

GENERATION OF LTB_4



The FDA Public Health Advisory: Long Acting Beta$_2$-Agonists (LABAs)

(Salmeterol and Formoterol)

- LABAs should not be the first medicine to treat asthma.
- LABAs should be added only if other asthma medicines do not control asthma (e.g. low to medium dose ICS).
- Do not stop using LABAs until you have discussed this with your health care provider.
- Do not use LABA to treat wheezing that has worsened.

Although LABAs decrease asthma episodes, one recent study has shown that these drugs may increase the chances of a severe asthma.

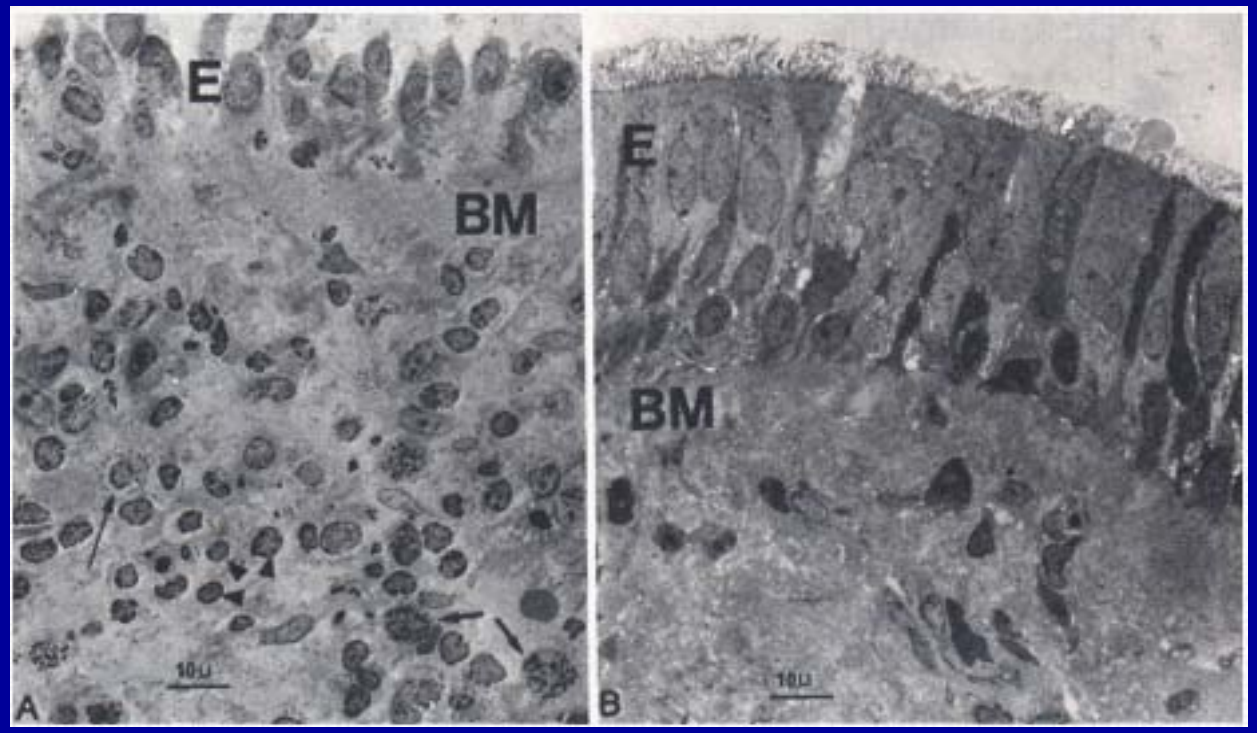
http://www.fda.gov/cder/drug/advisory/LABA.htm

MEDICATIONS

- Inhaled Corticosteroids (ICS)
- Long-acting Inhaled Beta $_2$ –Agonists (LABA)
- Combined Medications
- Cromolyn and Nedocromil
- Leukotrienes Modifiers
  - Montelukast
  - Zileutin
- Methylxanthines
- Immunoregulation
  - Allergy Shots
  - Xolair

Effects of Inhaled Corticosteroids on Inflammation

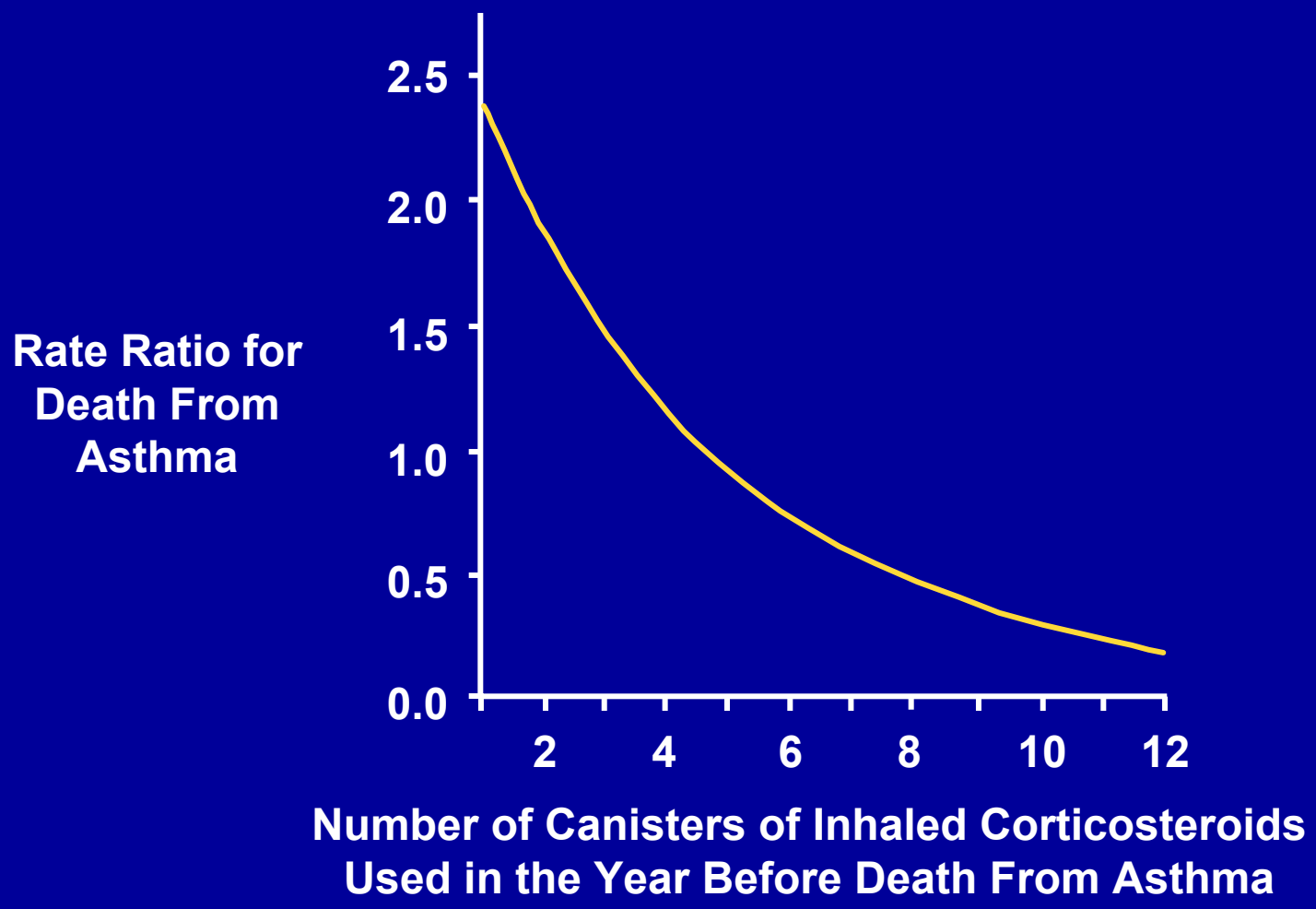
E = Epithelium BM = Basement Membrane



Before and after 3 months of treatment with budesonide 600 µg bid

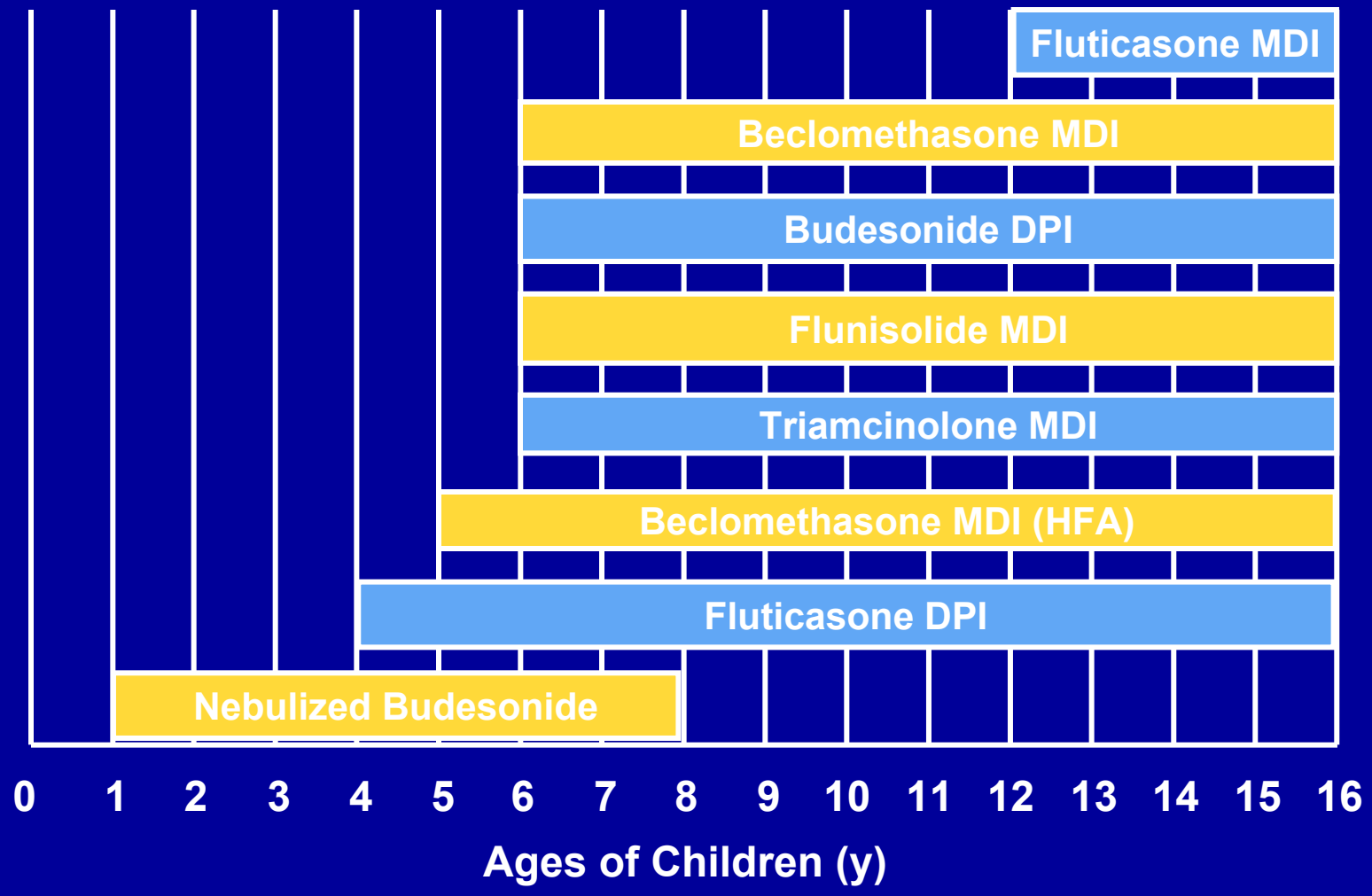
Laitinen. *J Allergy Clin Immunol.* 1992;90:32-42.

Low-Dose Inhaled Corticosteroids May Prevent Death From Asthma



Suissa et al. *N Engl J Med.* 2000;343:332-6.

Inhaled Corticosteroids Currently Approved by the FDA for Maintenance Treatment of Asthma



DPI = dry-powder inhaler; FDA = Food and Drug Administration; HFA = hydrofluoroalkane; MDI = metered-dose inhaler.

Basis for FDA Approval of Nebulized Budesonide in Young Children

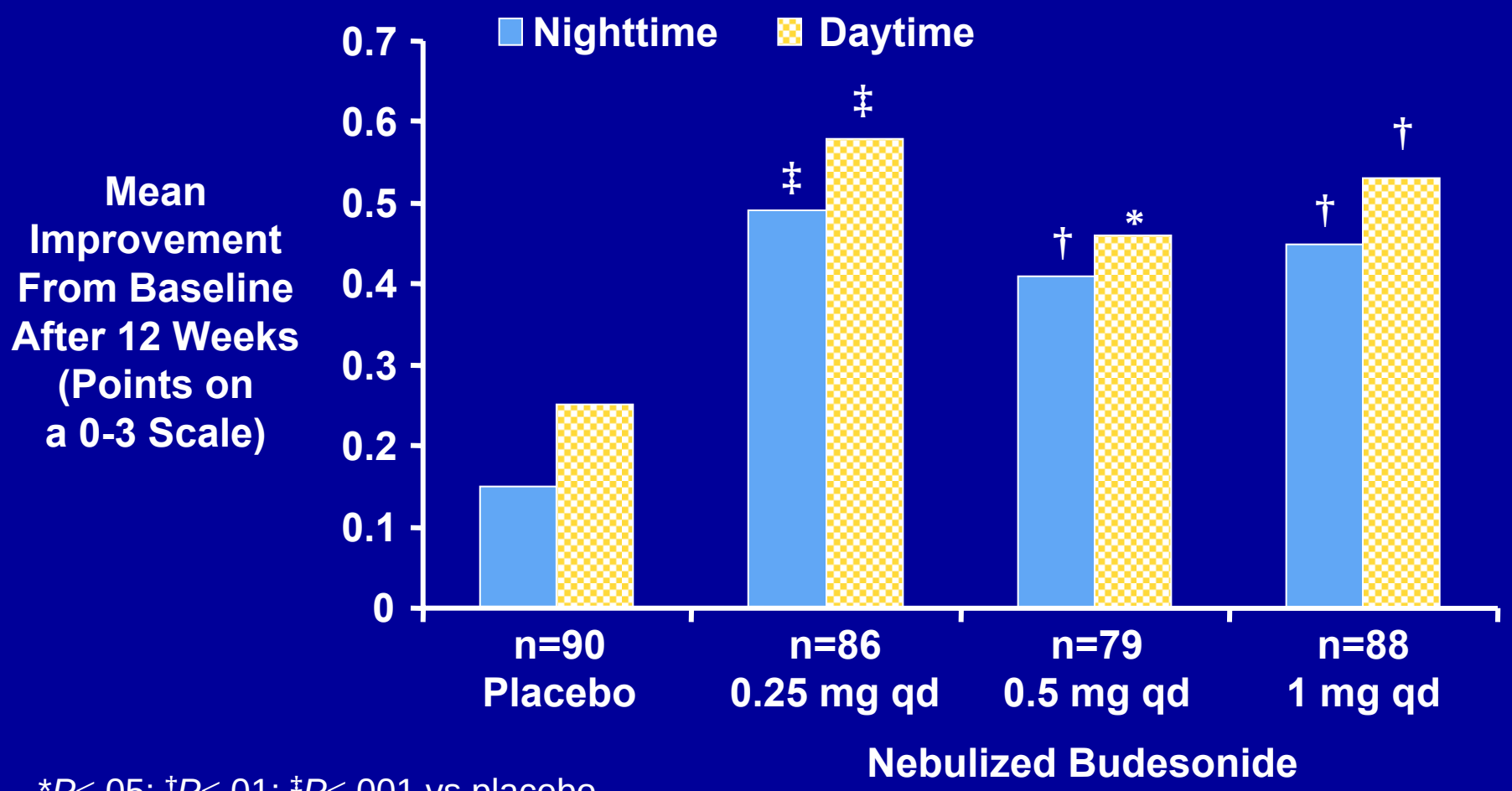
Reference	Age*	Asthma Dx	Prior ICS Use	Treatment Groups†
Kemp et al 1999	6 mo-8 y	Mild persistent	No	Placebo 0.25 mg qd 0.5 mg qd 1 mg qd
Shapiro et al 1998	4-8 y	Mild to Moderate persistent, PFTs required	Yes	Placebo 0.25 mg bid 0.5 mg bid 1 mg bid†
Baker et al 1999	6 mo-8y	Moderate persistent	Optional	Placebo 0.25 mg qd 0.25 mg bid 0.5 mg bid 1 mg qd

Dx = diagnosis; FDA = Food and Drug Administration; ICS = inhaled corticosteroid; PFT = pulmonary function tests.

*Nebulized budesonide is not FDA approved for children younger than 12 months; †Highest approved total daily dose in the United States is 1 mg.

Kemp et al. *Ann Allergy Asthma Immunol.* 1999;83:231-9; Shapiro et al. *J Allergy Clin Immunol.* 1998;102:789-96; Baker et al. *Pediatrics.* 1999;103:414-21.

Once-Daily Nebulized Budesonide: Effect on Asthma Symptom Scores



*$P \leq .05$; †$P \leq .01$; ‡$P \leq .001$ vs placebo.
Includes only patients 12 months to 8 years of age and up to a total daily dose of 1 mg.

Kemp et al. *Ann Allergy Asthma Immunol.* 1999;83:231-9; DA-RES-04. AstraZeneca LP.

Nebulized Budesonide: Summary of Pivotal Studies

- Improved nighttime and daytime asthma symptom scores
- Reduced need for daily bronchodilator treatment
- Improved lung function

Kemp et al. *Ann Allergy Asthma Immunol.* 1999;83:231-9; Shapiro et al. *J Allergy Clin Immunol.* 1998;102:789-96; Baker et al. *Pediatrics.* 1999;103:414-21.

Medications: Long-term Management of Asthma in Children

Does chronic use of inhaled corticosteroids improve long-term outcomes for children with mild or moderate persistent asthma compared with other asthma medications?

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

Medications: Long-term Management of Asthma in Children

"Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or leukotriene receptor antagonists are limited, but available evidence shows that none of these long-term control medications is as effective as inhaled corticosteroids in improving asthma outcomes."

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

Decreased Morning Serum Cortisol Levels in Children with Asthma Teated with Inhaled Fluticasone Propionate

- Eid N, Morton R, Olds B, Clark P, Sheikh S, Looney S.
- Pediatrics 2002;109:217-221

Decreased morning serum cortisol levels in children with asthma teated with inhaled fluticasone propionate

- Objective
  - To evaluate effects of fluticasone MDI with spacer device on HPA function in children with moderate to severe asthma
- Methods
  - Observational
  - 62 children x 2 years
    - 11.6 ± 2.9 years
    - 37 males, 25 females
- Funding
  - Non-pharmaceutical company funded
  - Self-supported

Measurements

- AM cortisol concentrations
  - After received constant FP dose $\geq$ 3 months
  - Resules: after receiving FP for 8 $\pm$ 5.2 months

- Patients with abnormal low morning cortisol (< 5.5 mcg/dl)
  - Switched to lower dose FP or another ICS
  - Follow-up am cortisol measurements
    - In 19/22 of patients

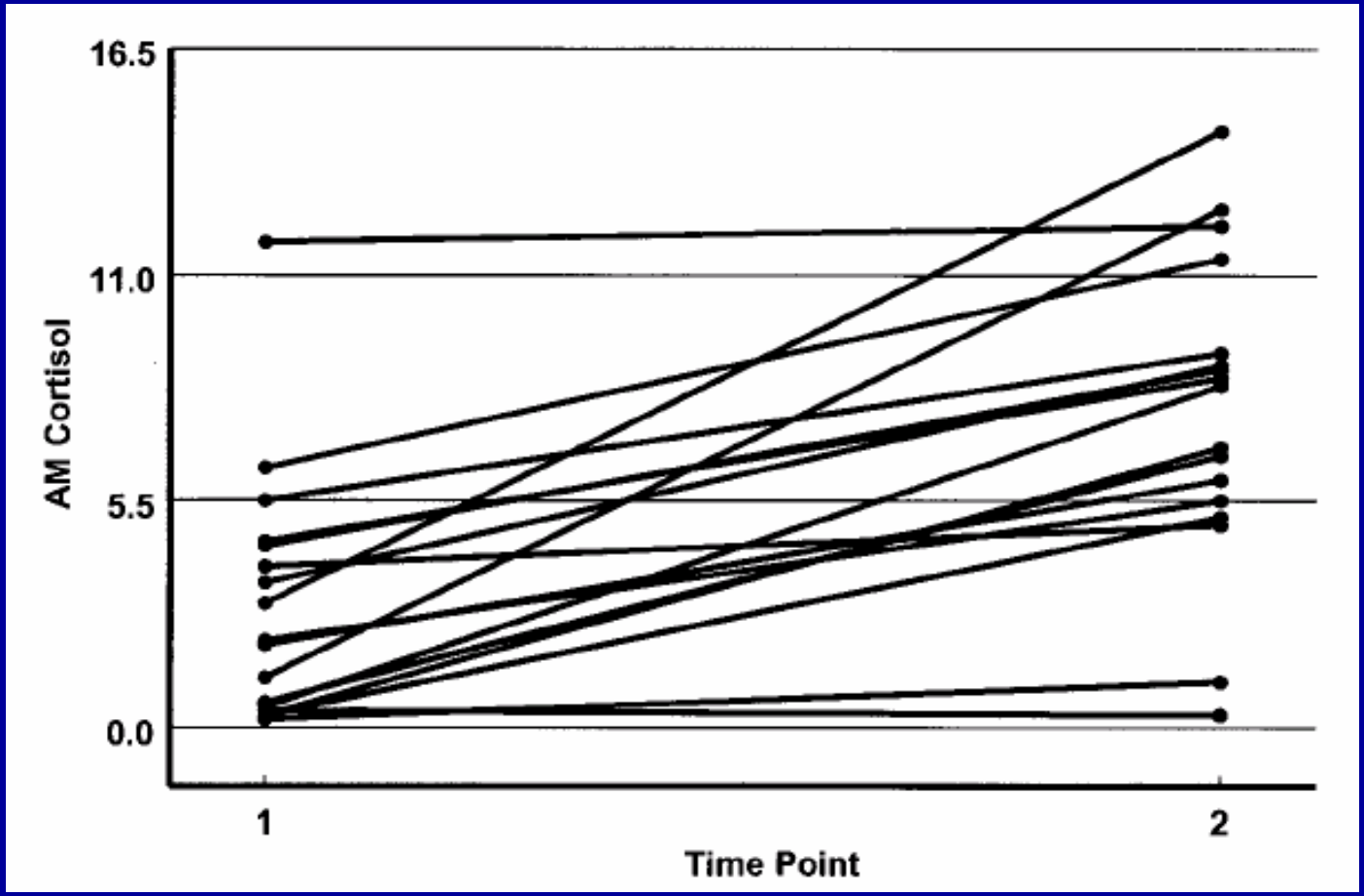
Effects of FP on AM Cortisol Levels

Dose mcg/day	*N*	*Abnormal N (%)*	*Last PO steroid* (mos)*	*Time on FP** (mons)*
176	6	1 (17%)	5.9	4.8
440	26	9 (35%)	5.9	8.6
≥ 880	28	12 (43%)	5.4	12.9
Total	60	22 (37%)	5.8	9.9

*** Time since last oral steroid dose**
**** Time receiving same dose of FP**

Eid et al. Pediatrics 2002; (Feb)109:217-21

Change in morning cortisol on repeat testing following switch



17/22 patients with 2nd cortisol measurement; 13 had normal cortisol on 2nd test.

Comparison of Inhaled Corticosteroid With Nedocromil

Long-term Effects of Budesonide or Nedocromil in Children With Asthma

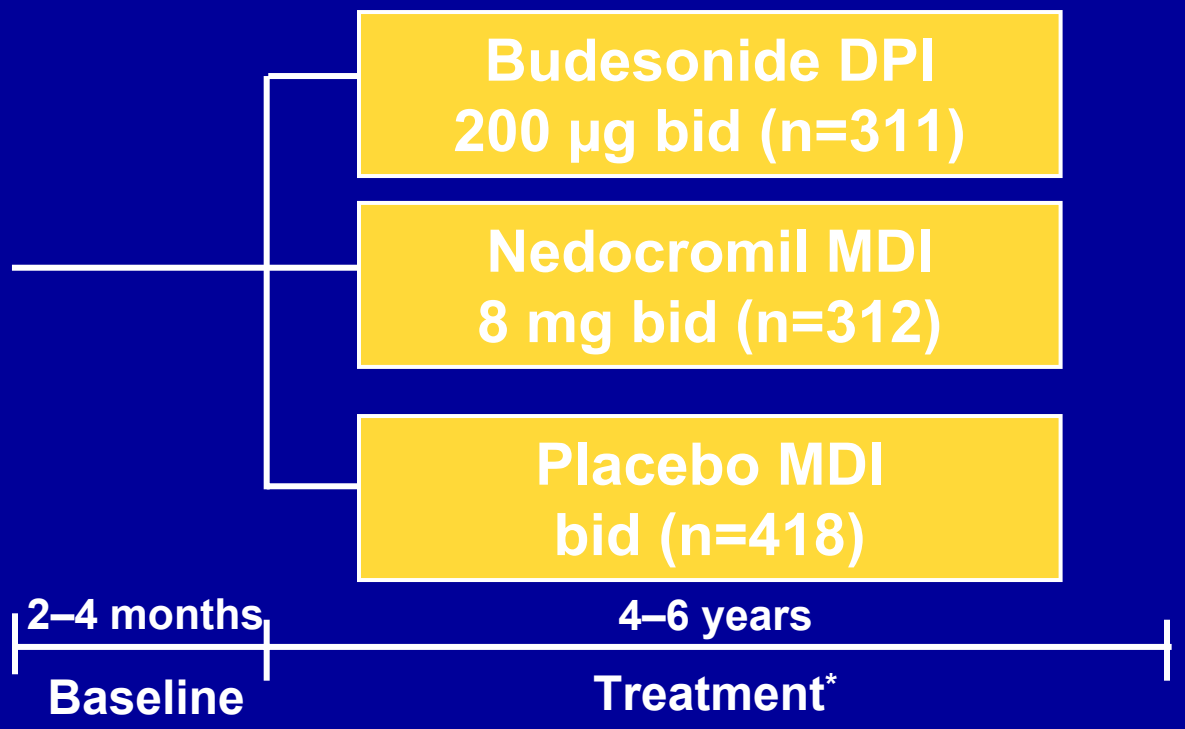
The Childhood Asthma Management Program Research Group

The New England Journal of Medicine

October 12, 2000; Volume 343:1054-63.

CAMP Study Design

Randomized, double-blind, multicenter study in children aged 5-12 years with mild to moderate asthma (n=1041)



CAMP = Childhood Asthma Management Program; DPI = dry-powder inhaler; MDI = metered-dose inhaler.
*All children used albuterol for asthma symptoms. Oral prednisone was allowed to treat asthma exacerbations, and beclomethasone dipropionate 168 µg bid could be added to study medication if asthma control was inadequate.

Childhood Asthma Management Program Research Group. *N Engl J Med.* 2000;343:1054-63.

CAMP Study Objectives

- Evaluated if continuous long-term treatment with an ICS or an inhaled noncorticosteroid could safely improve lung growth versus as-needed symptomatic treatment
- Lung growth assessed by the change in postbronchodilator percent predicted FEV_1
- Secondary outcomes: AHR, morbidity, physical growth, psychological development

AHR = airway hyperresponsiveness; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid.

Childhood Asthma Management Program (CAMP) Research Group. *N Engl J Med.* 2000;343:1054-63; CAMP. *Controlled Clin Trials.* 1999;20:91-120.

Patient Characteristics

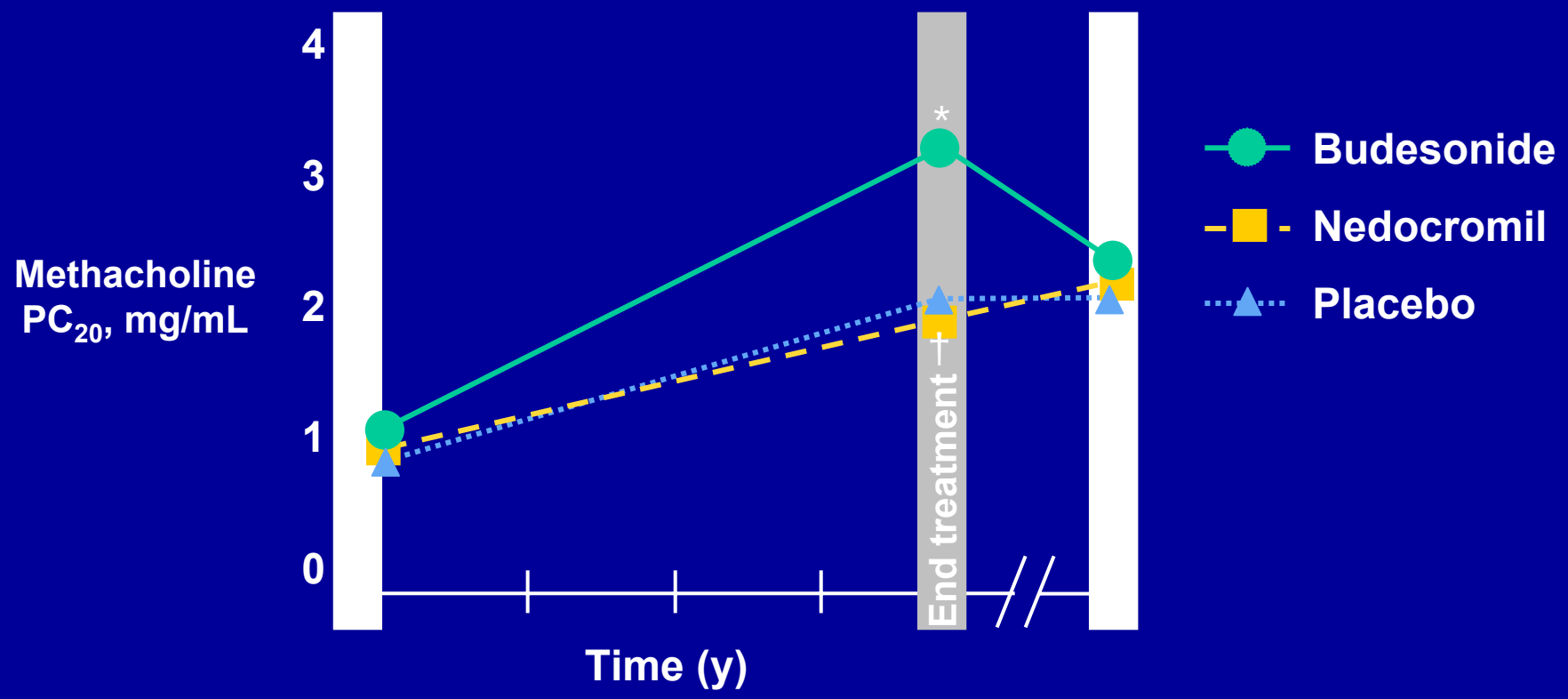
Characteristic	Budesonide (n=311)	Nedocromil (n=312)	Placebo (n=418)
Mean age, y ± SD	9.0 ± 2.1	8.8 ± 2.1	9.0 ± 2.2
Mean asthma duration, y ± SD	5.2 ± 2.6	5.0 ± 2.7	4.9 ± 2.7
Mean postbronchodilator % predicted FEV_1 ± SD	103.2 ± 13.2	102.3 ± 12.7	103.3 ± 12.2
Asthma medications used in 6 mo before enrollment, %			
Cromolyn or nedocromil	42.8	47.4	38.3
Inhaled corticosteroid	40.5	36.5	35.9
Oral corticosteroid	34.4	30.1	38.8

FEV_1 = forced expiratory volume in 1 second.

Childhood Asthma Management Program Research Group. *N Engl J Med.* 2000;343:1054-63.

Long-term Effects of Budesonide or Nedocromil in Children With Asthma

Airway responsiveness measured by the concentration of methacholine that caused a 20% decrease in FEV_1



FEV_1 = forced expiratory volume in 1 second. *P<.001 vs placebo; †P=.97 vs placebo.

Childhood Asthma Management Program Research Group. *N Engl J Med.* 2000;343: 1054-63; NAPS document no. 05569, c/o Microfiche Publications, West Hempstead, NY.

Montelukast Monotherapy vs Combination With an Inhaled Corticosteroid

- 642 adults with chronic (≥1 year) asthma
- Inadequate control with 200 μg of beclomethasone twice daily
- 4 treatment groups, double-blind, double-dummy
  - 400-μg beclomethasone + 10-mg montelukast
  - 400-μg beclomethasone + placebo tablet
  - 10-mg montelukast + placebo inhaler
  - Placebo tablet + placebo inhaler
- 16-week treatment period with 4-week run-in

Laviolette et al. *Am J Respir Crit Care Med.* 1999;160:1862-8.

Clinical Outcomes According to Treatment Group

Changes in Daily Diary-Card Measures	Mean Value			*P* Value	
	BUD (n=311)	NED (n=312)	PBO (n=418)	BUD vs PBO	NED vs PBO
Symptom scores	-0.44	-0.38	-0.37	.005	.80
Morning peak flow, L/min	131	131	132	.86	.82
Episode-free days, n/mo	11.3	9.3	9.3	.01	.97
Albuterol use, puffs/wk	-7.4	-5.7	-5.3	<.001	.42
Night awakenings, n/mo	-0.7	-0.6	-0.6	.14	.48

BUD = budesonide; NED = nedocromil; PBO = placebo.

Childhood Asthma Management Program Research Group. *N Engl J Med.* 2000;343:1054-63.

Medications: Long-term Asthma Management in Children

What are the long-term adverse effects of chronic inhaled corticosteroid use in children on vertical growth, bone mineral density, ocular toxicity, and suppression of the hypothalamic pituitary adrenal axis?

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

Safety of Long-term Inhaled Corticosteroid Use in Children

Low to medium doses of ICS do not have frequent clinically significant or irreversible adverse effects on:

- Long-term growth
- Bone mineral density
- Ocular toxicity (cataracts and glaucoma)
- Hypothalamic pituitary adrenal axis function

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

MEDICATIONS

- Inhaled Corticosteroids (ICS)
- Long-acting Inhaled Beta $_2$ –Agonists (LABA)
- Combined Medications
- Cromolyn and Nedocromil
- Leukotrienes Modifiers
  - Montelukast
  - Zileutin
- Methylxanthines
- Immunoregulation
  - Allergy Shots
  - Xolair

Moderate Persistent Asthma: Treatment Options

Children ≤5 Years

- Medium-dose ICS (Evidence D)*
- Low-dose ICS plus
  - LABA (Evidence B, extrapolation from studies in older children & adults)*
  - LTM (SRE Evidence B)
  - Theophylline (SRE Evidence B)

Children >5 Years & Adults

- Low- to medium-dose ICS plus
  - LABA (SRE Evidence A)*
  - LTRA (SRE Evidence B)
  - Theophylline (SRE Evidence B)
- Increase ICS dose in medium range

ICS = inhaled corticosteroid; LABA = long-acting β_2-adrenergic agonist; LTM = leukotriene modifier; LTRA = leukotriene receptor antagonist; SRE = systematic review of the evidence.
*Preferred treatment options.

NAEPP. Guidelines update 2002. *J Allergy Clin Immunol.* 2002;110(pt 2):S141-219.

MEDICATIONS

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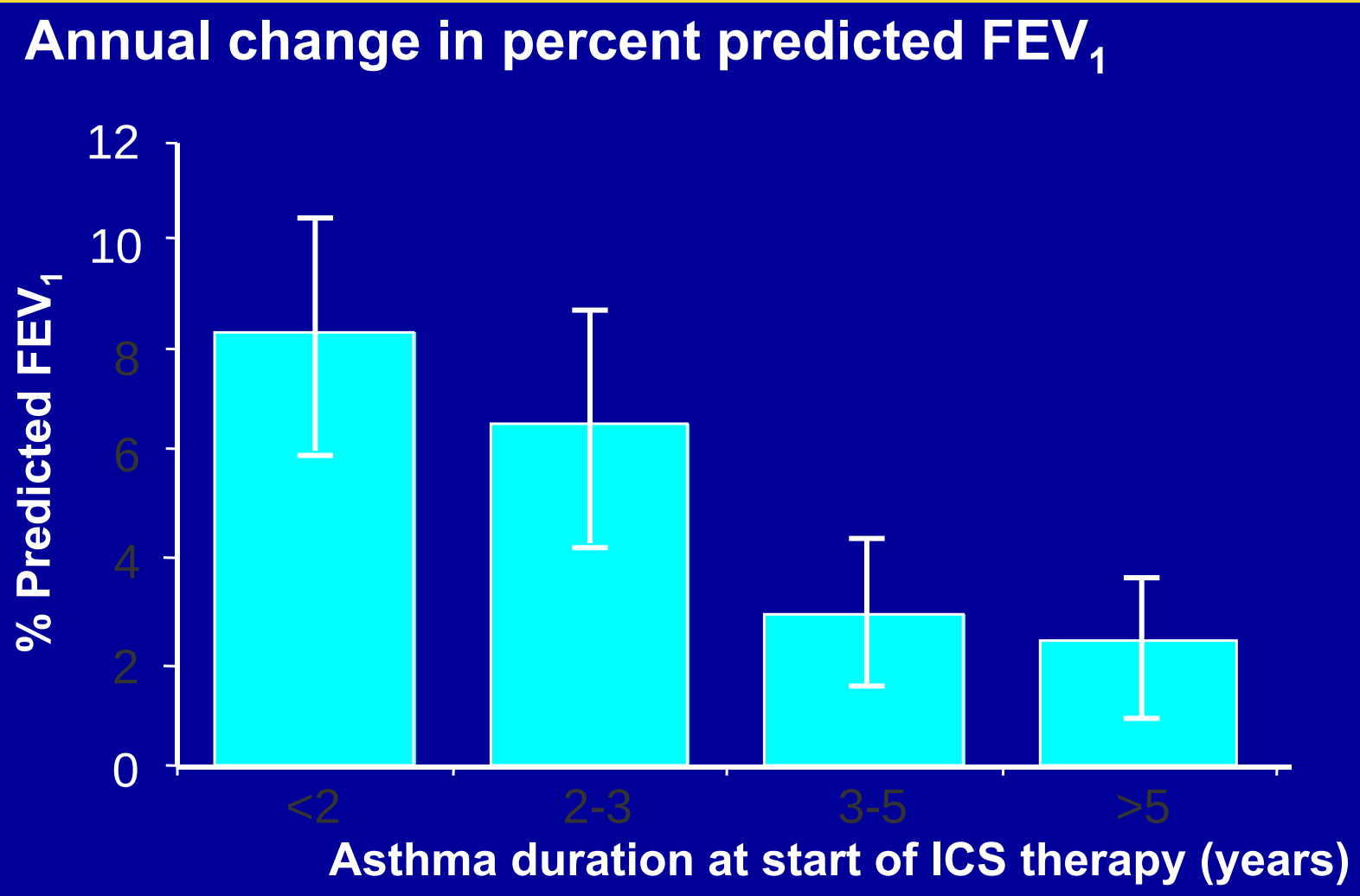
  - Allergy Shots
  - Xolair

Early Use of Inhaled Corticosteroids



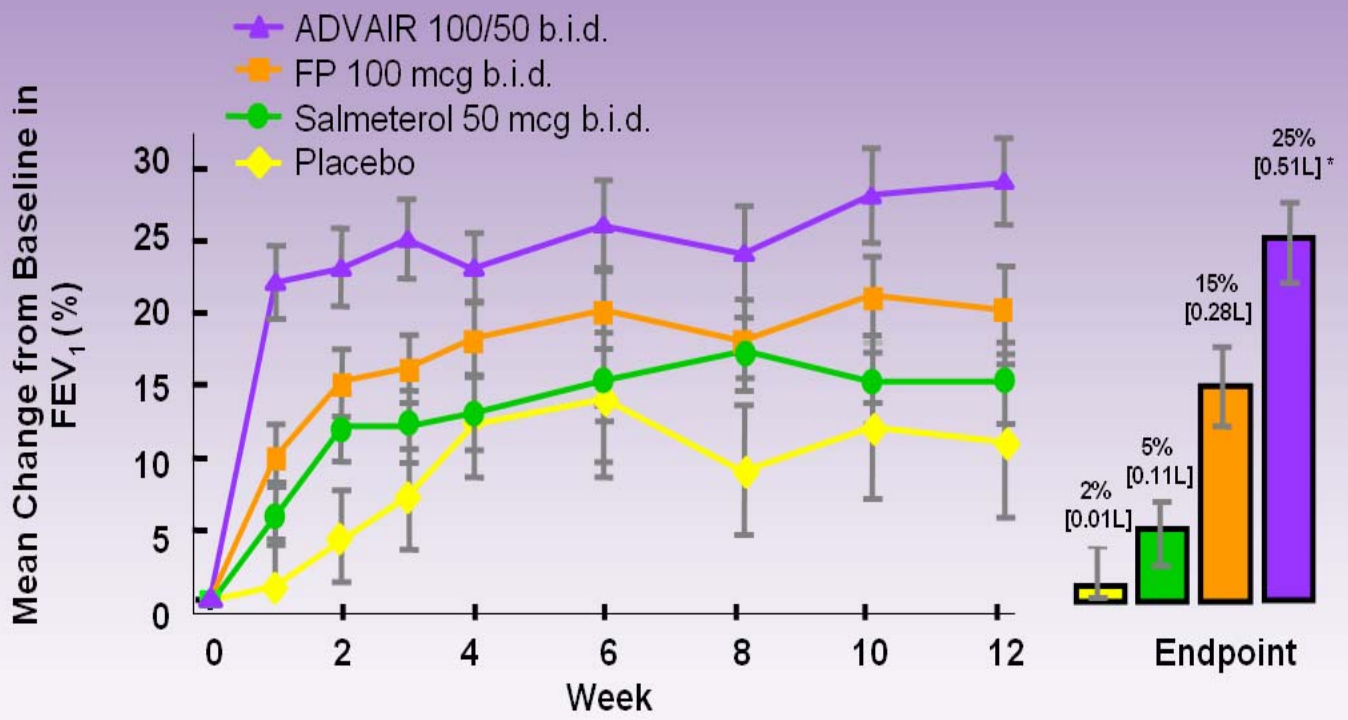
Agertoft and Pedersen. *Respir Med* 1994;88:373-381.

ADVAIR 100/50: Experience in Children with Asthma 4 to 11 Years Old

- ADVAIR 100/50 was well-tolerated in clinical trials
- The safety profile of ADVAIR 100/50 was studied in a 12-week trial of 203 children who were symptomatic on a low-dose ICS
- The primary objective of this study was to determine the safety of ADVAIR 100/50 compared with fluticasone propionate (FP) 100 mcg
- ADVAIR 100/50 had a similar safety profile to FP 100 mcg
- A secondary efficacy measure of FEV_1 in children 6 to 11 years old showed an increase from 1.70 L at baseline to 1.88 L at endpoint for patients receiving ADVAIR 100/50 and from 1.65 L to 1.77 L for patients receiving FP 100 mcg

Advair Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline; April 2004.

ADVAIR 100/50 Significantly Improved FEV_1 in Patients 12 Years and Older Previously Treated with ICS or Salmeterol



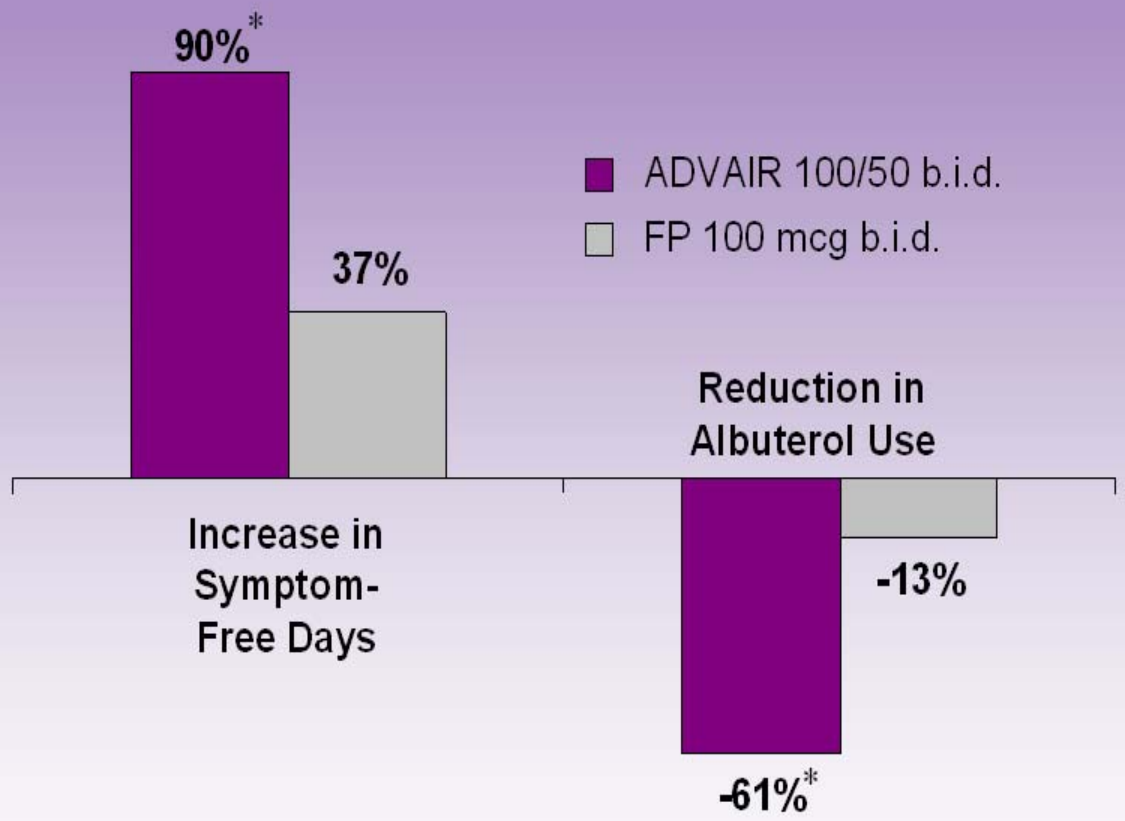
*$P \leq 0.008$ vs FP, salmeterol, and placebo at Endpoint.

Baseline values were ADVAIR 100/50: 2.17 L, FP: 2.11 L, salmeterol: 2.13 L, placebo: 2.15 L.

Results of a 12-week, randomized, double-blind, placebo-controlled study of 356 patients with mild-to-moderate asthma previously treated with p.r.n. albuterol and either an ICS or salmeterol.

Kavuru et al. *J Allergy Clin Immunol*. 2000;105:1108-1116.

Mean Improvements in Symptom-Free Days and Albuterol Use in Patients 12 Years and Older



Both groups demonstrated improvement in nights with no awakenings (*P*=NS between the 2 groups).

*$P \leq 0.025$ ADVAIR 100/50 vs FP at Endpoint.

Baseline values: 25.2% symptom-free days and 3.1 puffs/day of albuterol for ADVAIR 100/50; and 19.4% symptom-free days and 3.1 puffs/day for FP.

Kavuru et al. *J Allergy Clin Immunol.* 2000;105:1108-1116.

MEDICATIONS

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  - Allergy Shots
  - Xolair

5-Lipoxygenase Pathway

In vitro **data do not necessarily correlate with clinical efficacy**

Cysteinyl Leukotrienes

Leukotriene C_4

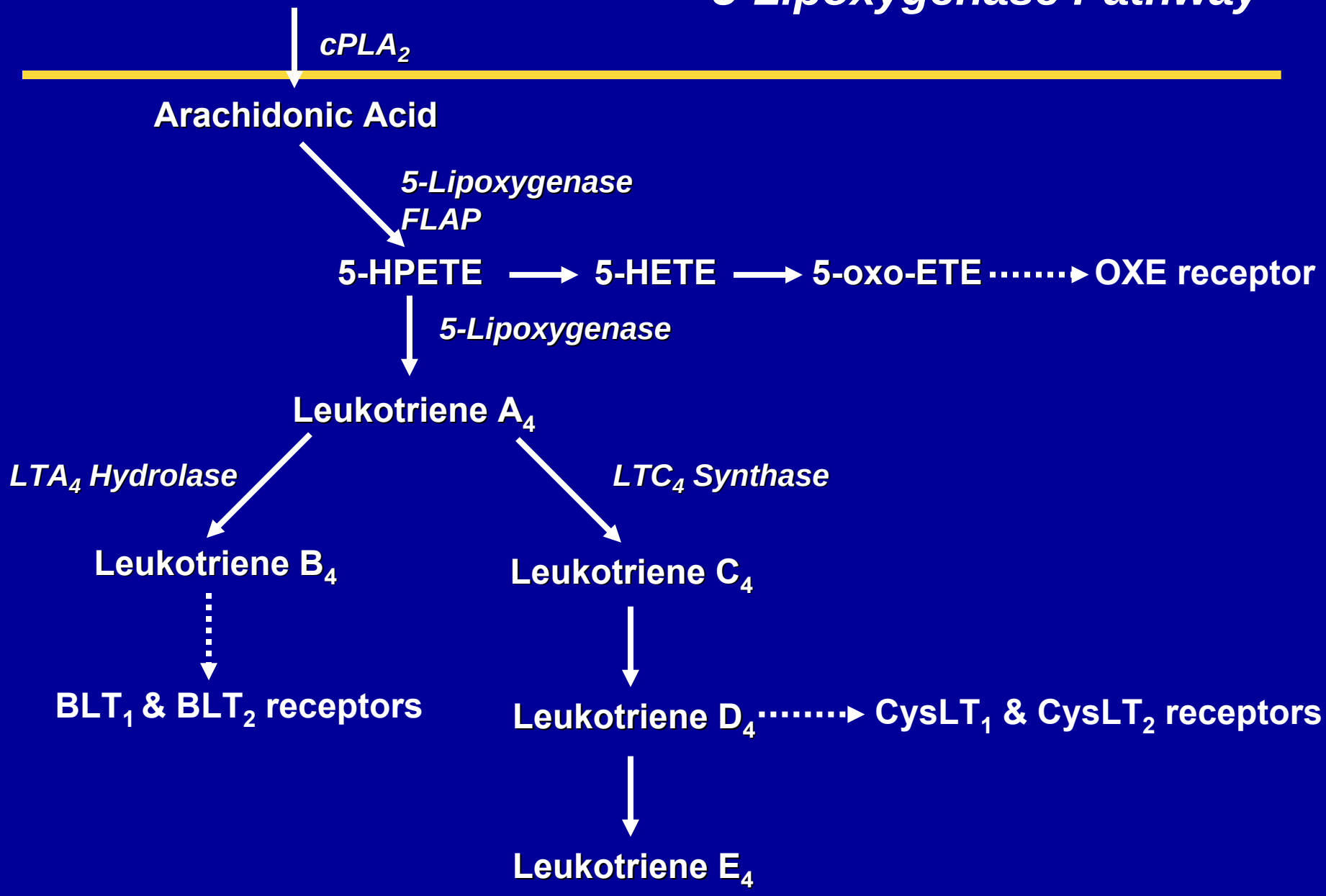
↓

Leukotriene D_4 ⋯⋯► $CysLT_1$ & $CysLT_2$ receptors

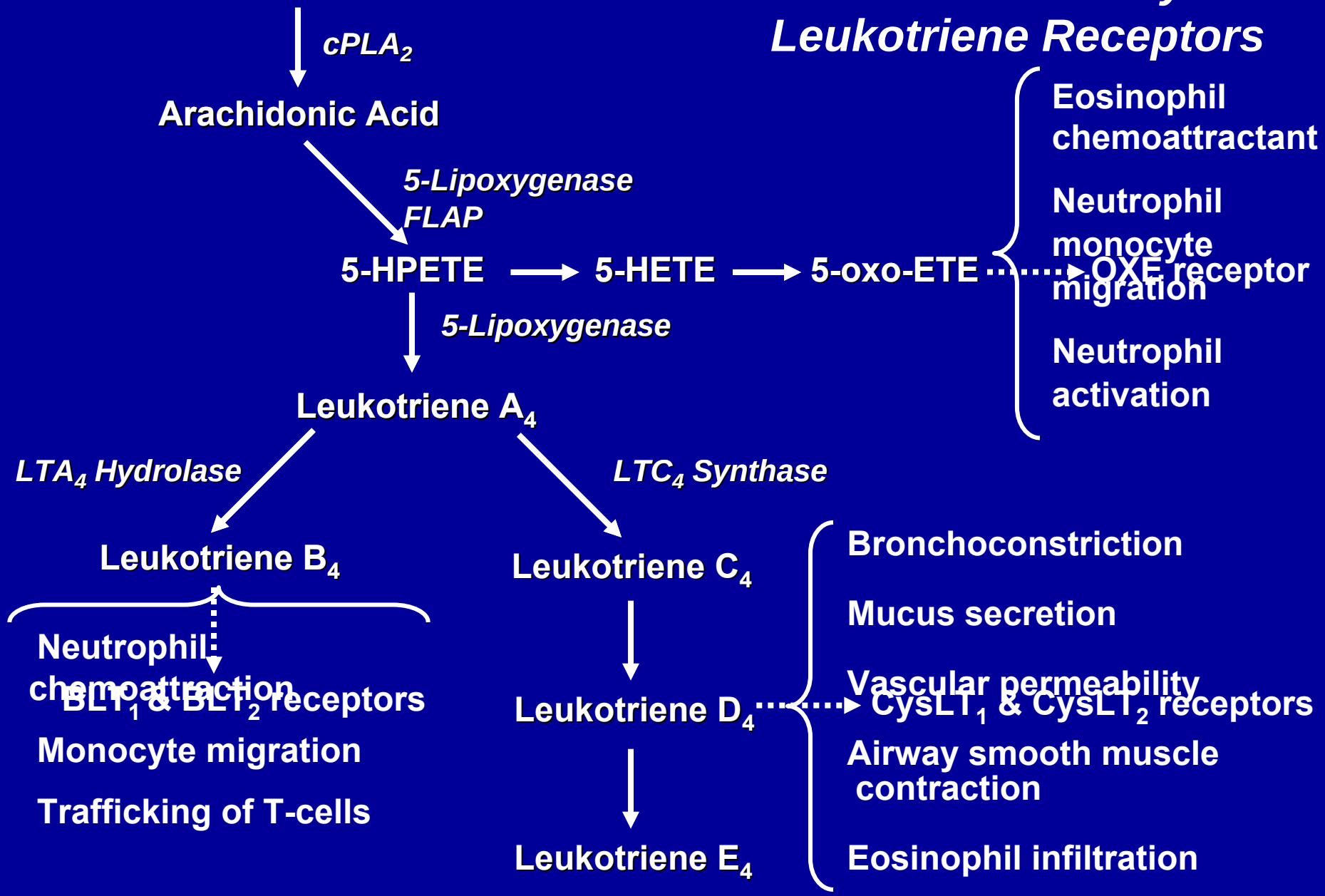
↓

Leukotriene E_4

5-Lipoxygenase Pathway

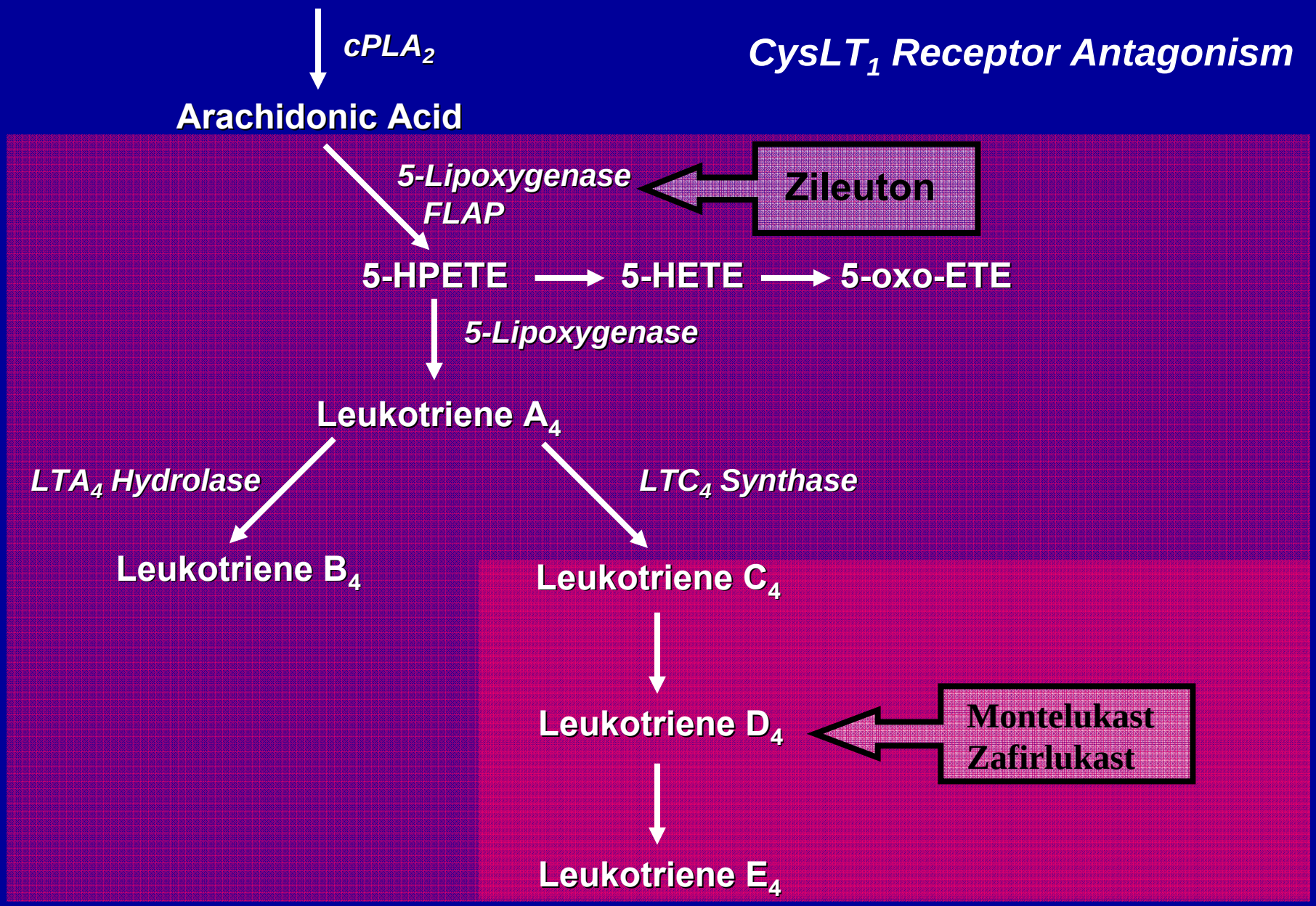


5-LO Activates Key Leukotriene Receptors



5-Lipoxygenase Inhibition

$CysLT_1$ Receptor Antagonism



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  - Allergy Shots
  - Xolair

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3–10)

Medication	Dosages		
	Adult Dose	Child Dose*	Comments
Systemic Corticosteroids	*(Dosages and comments apply to all three corticosteroids)*		
Prednisone Methylprednisolone Prednisolone	120–180 mg/day in 3 or 4 divided doses for 48 hours, then 60–80 mg/day until PEF reaches 70% of predicted or personal best	1 mg/kg every 6 hours for 48 hours then 1–2 mg/kg/day (maximum = 60 mg/day) in 2 divided doses until PEF 70% of predicted or personal best	For outpatient "burst" use 40–60 mg in single or 2 divided doses for adults (children: 1–2 mg/kg/day, maximum 60 mg/day) for 3–10 days.