

Ambulatory Asthma Management

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Conflicts of Interest

None.

Goals of Modern Asthma Care

- Minimize symptoms/maximize function
- Prevent asthma attacks
- Minimize medication side-effects

Challenges of Modern Asthma Care

- Equitable distribution of care throughout society
- Availability of low-cost (generic) medications
- Prevention of decline in lung function over time

Lecture Outline

- I. Defining asthma control
- II. Achieving asthma control: A five-point plan
 - A. Making the correct diagnosis
 - B. Modifying environmental inciters
 - C. Medications to control asthma
 - D. Plan for dealing with asthmatic attacks
 - E. Specialist consultation

Staging Asthma Severity

Stage	Daytime Symptoms	Nighttime Symptoms	Lung Function (FEV ₁ or PEFR)
<i>Intermittent</i>	≤2 days/wk	≤2 nights/mo.	≥80
<i>Mild persistent</i>	3-6 days/wk	3-4 nights/mo.	≥80
<i>Moderate persistent</i>	Daily	≥5 nights/mo.	>60 - <80%
<i>Severe persistent</i>	Continual	Frequent	≤60%

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Assessing Asthma Control

Two “Domains” :

- **Current impairment**
 - Symptoms (daytime, nighttime, and frequency of use of rescue bronchodilator)
 - Exercise limitation
 - Lung function
- **Future risk**
 - More than 1 oral steroid course in last year

Asthma Control Test

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
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2. During the past **4 weeks**, how often have you had shortness of breath?

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
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3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

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
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4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

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
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5. How would you rate your **asthma** control during the **past 4 weeks**?

Not controlled at all	①	Poorly controlled	②	Somewhat controlled	③	Well controlled	④	Completely controlled	⑤
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SCORE

TOTAL

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SCORE

TOTAL

Well-controlled asthma: ≥ 20

Concept of Asthma Control

In patients on regular controller medication:

- **Is asthma poorly controlled?** If yes, *step up* therapy.
- **Is asthma well controlled?** If yes, continue current treatment or *step down* therapy.

Achieving Asthma Control

The Five-Point Plan:

- A. *Making the correct diagnosis***
- B. Modifying environmental inciters
- C. Medications to control asthma
- D. Plan for dealing with asthmatic attacks
- E. Specialist consultation

Case Example

A 27 year-old woman, mother of two, finds that every “cold” settles into her chest, with paroxysmal coughing, a “wheezy cough,” and cough that lingers for weeks. She reports a history of eczema as a child and mild symptoms of seasonal allergic rhinitis.

Establishing the Correct Diagnosis

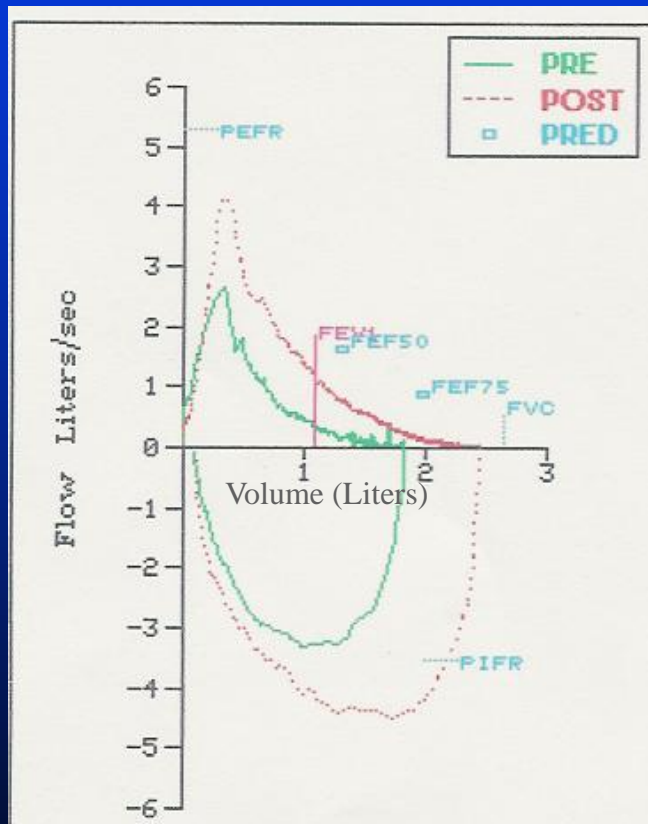
- Characteristic history
 - episodic symptoms
 - characteristic triggers
 - characteristic response to medications
- Characteristic examination
 - diffuse musical expiratory wheezes
- Diagnostic testing

Pulmonary Function Testing

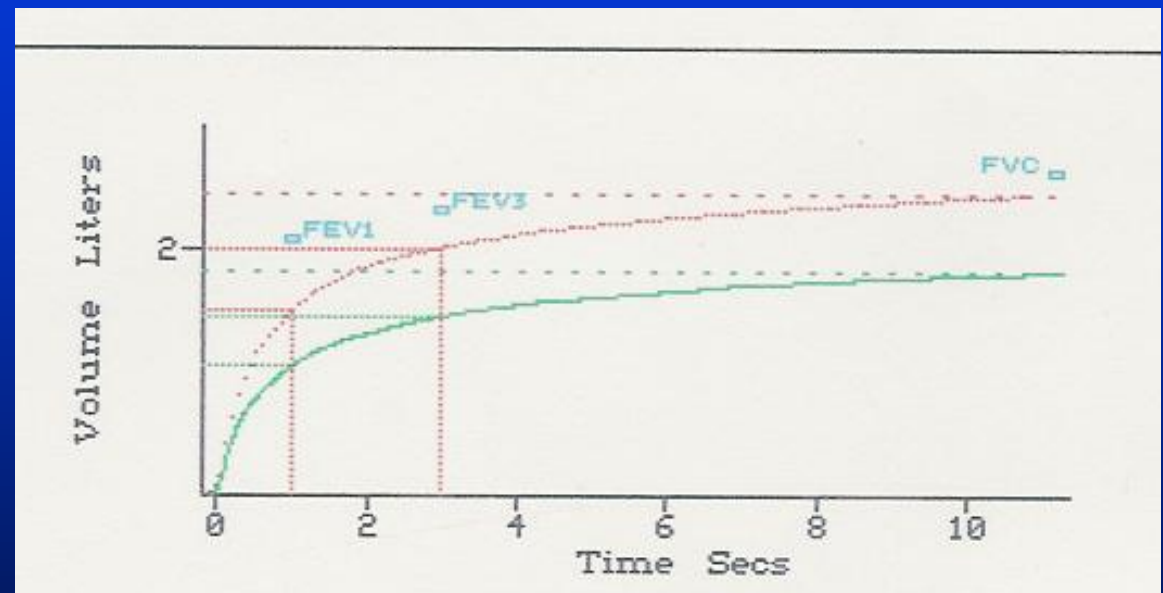
Variable expiratory airflow obstruction

- Varies over time
- Improves following bronchodilator
- Can be induced by provocative stimuli
 - e.g., methacholine

Spirometry/Flow-Volume Curve



Flow-Volume Curve



Spirometry (Volume-Time Curve)

Interpreting PFTs

Significant bronchodilator response:

- Increase in FEV_1 of 12% and
- Absolute increase of 200 ml

“Asthmatic response”:

- Variably defined as 15% or 20% increase in FEV_1 following BD

Potential Bio-Markers of Airway Inflammation in Asthma

- Exhaled nitric oxide
- Sputum eosinophilia
- Exhaled breath condensate



NiOx Mino

Achieving Asthma Control

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“Inciters” of Asthmatic Inflammation

“Inciters” both trigger asthmatic symptoms *and* induce increased asthmatic airway inflammation:

- Cigarette smoking
- Viral respiratory tract infections
- Inhaled aeroallergens

Common Aeroallergens

- Furry animals
- Dust mites
- Mold
- Cockroaches
- Pollens

Common Aeroallergens

- Furry animals
- Dust mites
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- Pollens

Diagnostic Testing:

Allergy skin tests

Blood tests (RAST)

Role of Inhaled Allergens

Allergic Sensitivity (Atopy)

+

Intense Allergen Exposure



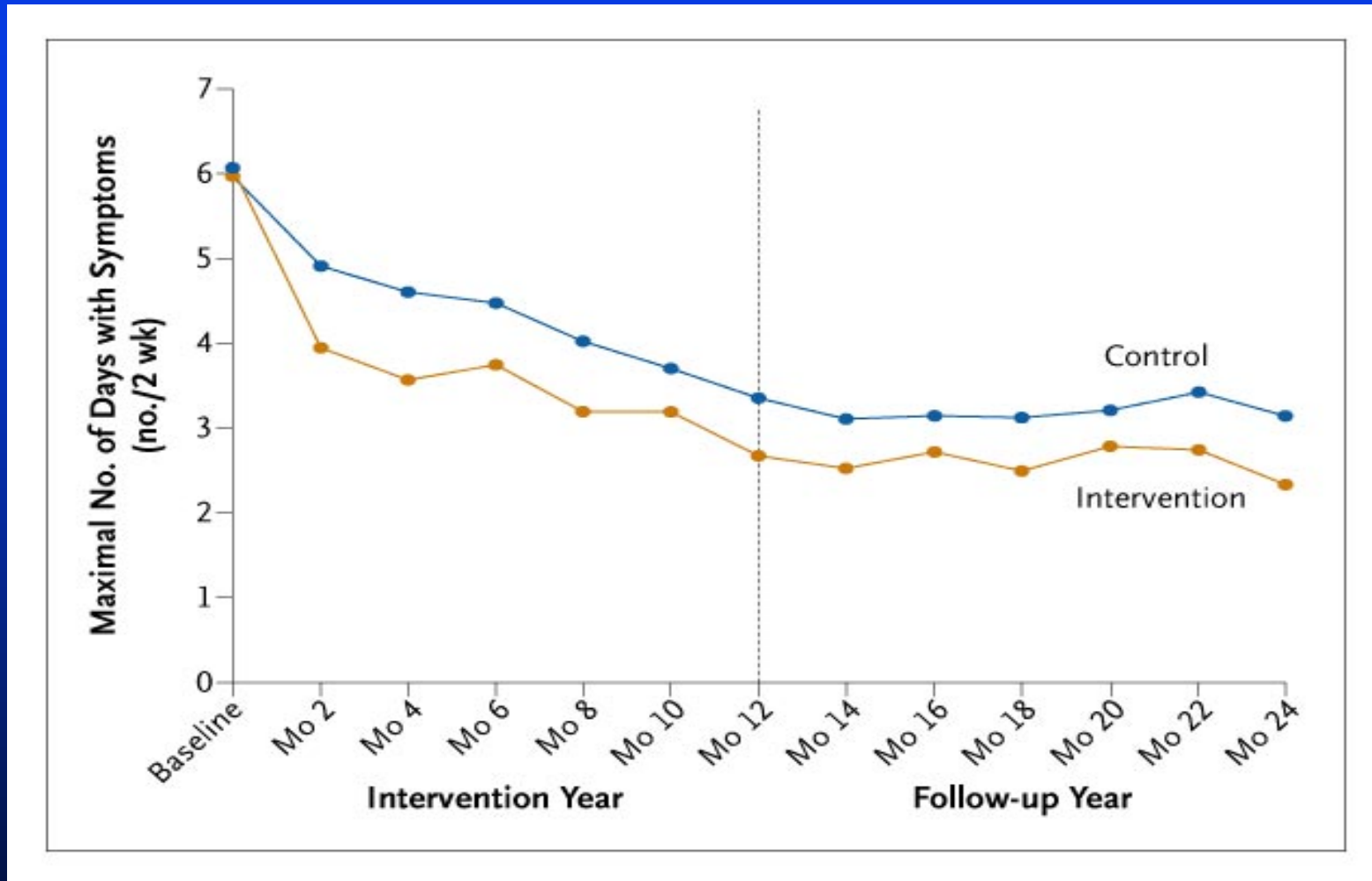
More Severe Asthma

ORIGINAL ARTICLE

Results of a Home-Based Environmental Intervention among Urban Children with Asthma

Wayne J. Morgan, M.D., C.M., Ellen F. Crain, M.D., Ph.D.,
Rebecca S. Gruchalla, M.D., Ph.D., George T. O'Connor, M.D.,
Meyer Kattan, M.D., C.M., Richard Evans III, M.D., M.P.H.,
James Stout, M.D., M.P.H., George Malindzak, Ph.D., Ernestine Smartt, R.N.,
Marshall Plaut, M.D., Michelle Walter, M.S., Benjamin Vaughn, M.S.,
and Herman Mitchell, Ph.D., for the Inner-City Asthma Study Group*

Mean Maximal Number of Days with Symptoms for Every Two-Week Period before a Follow-up Assessment during the Two Years of the Study



Morgan, W. J. et al. *N Engl J Med* 2004;351:1068-1080.

The Environmental Intervention

- 6 educational modules: dust mites; cigarette smoking; pets; cockroaches; rodents; and mold.
- Equipment and support:
 - Allergen-impermeable bed wraps
 - HEPA-filtered vacuum cleaners
 - HEPA room air filter
 - Cockroach extermination

Achieving Asthma Control

The Five-Point Plan:

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Modern Therapeutic Paradigm

Controllers:

- Inhaled steroids
- Long-acting inhaled beta-agonists
- Leukotriene blockers
- Biologics (anti-IgE)

Quick-Relievers:

- Quick-acting beta-agonist bronchodilators

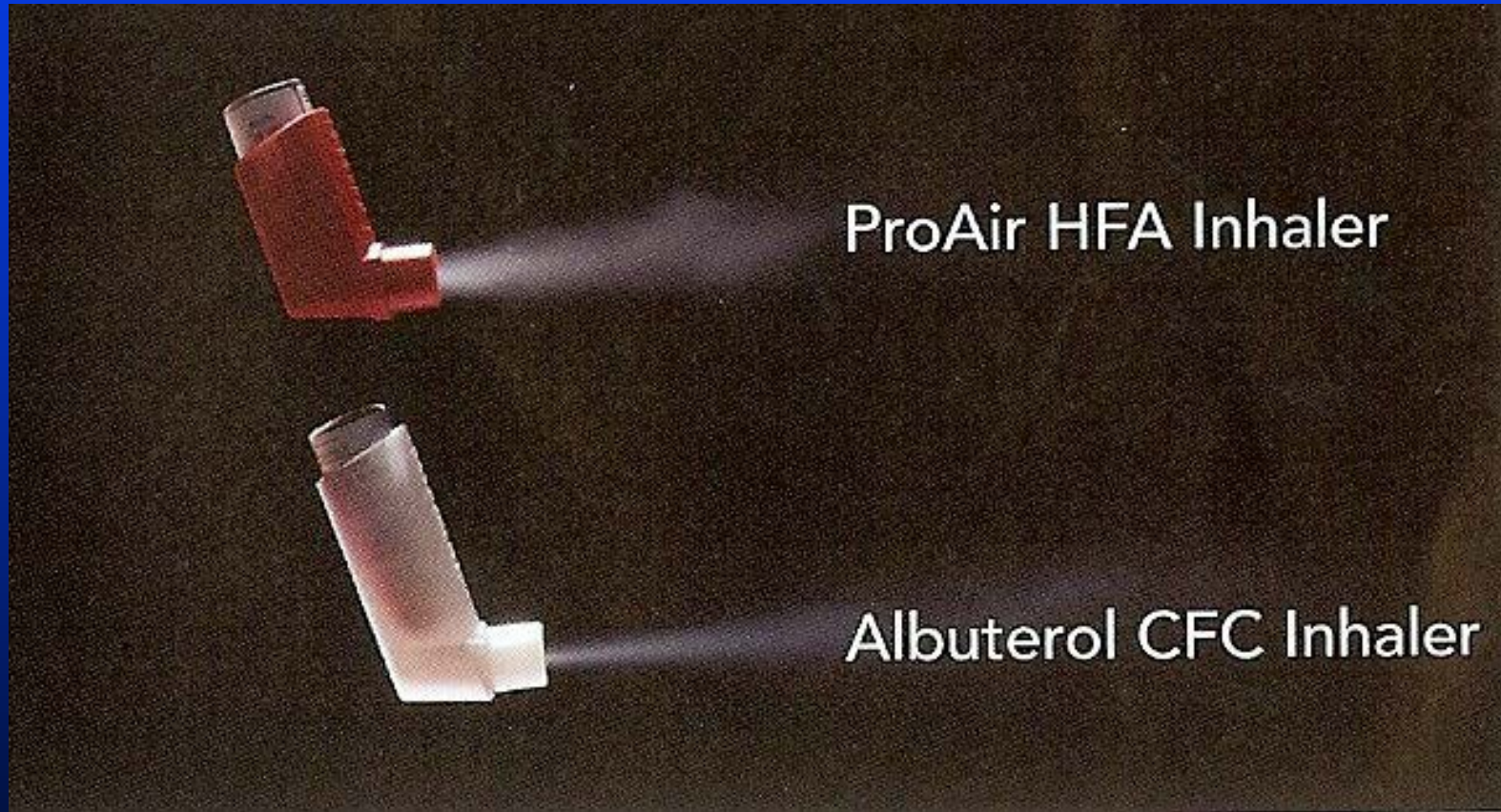
Step 1 (Intermittent Asthma)

- Short-acting bronchodilator as needed
- Short-acting bronchodilator prior to exercise

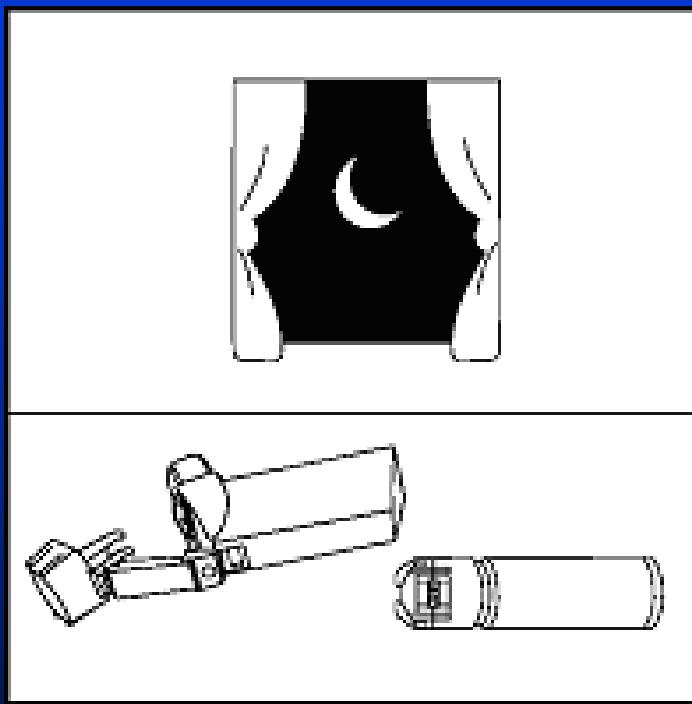
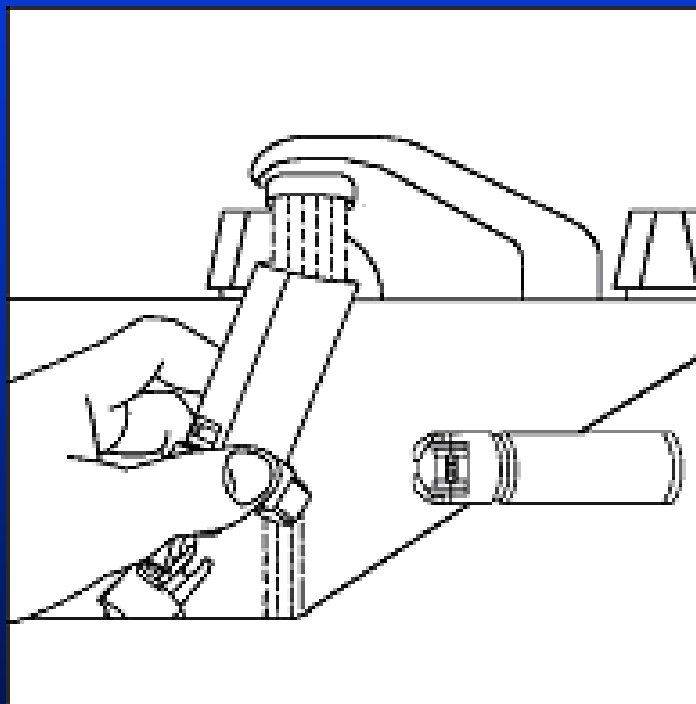
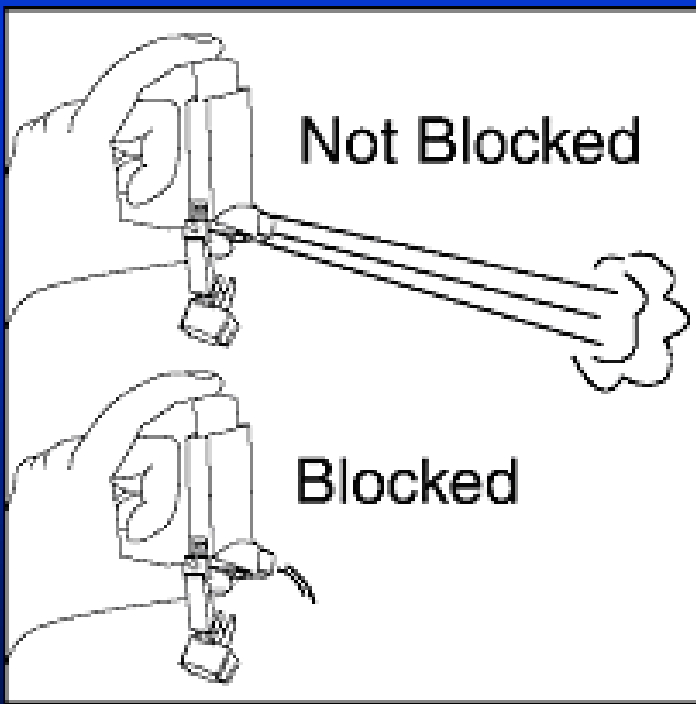
Short-Acting Beta-Agonists

- Albuterol MDI [ProAir, Proventil, Ventolin]
- Albuterol DPI (Breath-Actuated) [ProAir]
- Levalbuterol (single-isomer of albuterol) [Xopenex]

MDI Plume



Cleaning HFA-Driven MDIs



Step 2 (Mild Persistent Asthma)

- Preferred: Low-dose inhaled corticosteroid
- Alternatives:
 - Leukotriene receptor antagonists

Inhaled Steroid Preparations

		<u>mcg/puff</u>
• Budesonide DPI*	(<i>Pulmicort</i>)	90, 180
• Mometasone DPI*	(<i>Asmanex</i>)	110, 220
• Beclomethasone MDI-HFA*	(<i>Qvar</i>)	40, 80
• Fluticasone MDI-HFA	(<i>Flovent</i>)	44, 110, 220
• Fluticasone DPI	(<i>Flovent Diskus</i>)	50, 100, 250
• Fluticasone furoate DPI *	(<i>Arnuity</i>)	100, 200
• Ciclesonide MDI-HFA*	(<i>Alvesco</i>)	80, 160
• Flunisolide MDI-HFA	(<i>Aerospan</i>)	80

* *category B in pregnancy*

* *approved for once-daily dosing*

* *small particle size*

The NEW ENGLAND JOURNAL *of* MEDICINE

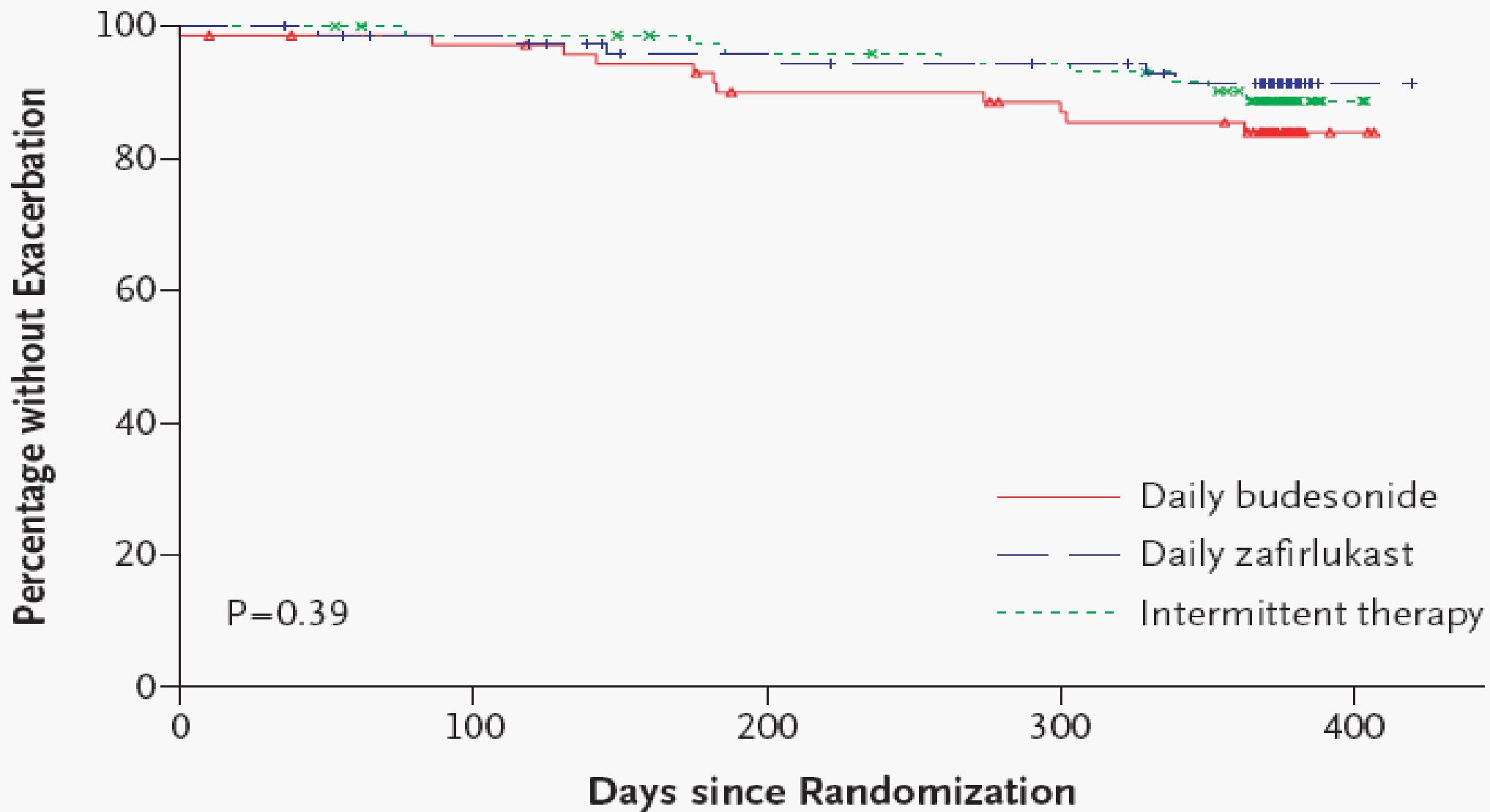
ESTABLISHED IN 1812

APRIL 14, 2005

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Daily versus As-Needed Corticosteroids for Mild Persistent Asthma

Homer A. Boushey, M.D., Christine A. Sorkness, Pharm.D., Tonya S. King, Ph.D., Sean D. Sullivan, Ph.D., John V. Fahy, M.D., Stephen C. Lazarus, M.D., Vernon M. Chinchilli, Ph.D., Timothy J. Craig, D.O., Emily A. Dimango, M.D., Aaron Deykin, M.D., Joanne K. Fagan, Ph.D., James E. Fish, M.D., Jean G. Ford, M.D., Monica Kraft, M.D., Robert F. Lemanske, Jr., M.D., Frank T. Leone, M.D., Richard J. Martin, M.D., Elizabeth A. Mauger, Ph.D., Gene R. Pesola, M.D., M.P.H., Stephen P. Peters, M.D., Ph.D., Nancy J. Rollings, M.Ed., Stanley J. Szefler, M.D., Michael E. Wechsler, M.D., and Elliot Israel, M.D., for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network



Intermittent Inhaled Steroids in Mild Asthma

Concept: Regular use of inhaled steroid during period of increased symptoms only

Benefits: Cost, convenience, adherence, fewer side effects

Potential disadvantage: Comprehension of concept of intermittent (not p.r.n.) use

Leukotriene-Modifying Drugs

- Leukotriene receptor blockers
 - Montelukast (*Singulair*)
 - Zafirlukast (*Accolate*)
- Lipoxygenase inhibitor
 - Zileuton (*Zyflo*)

Arachidonic Acid Pathway

Membrane Phospholipids



Phospholipase A₂

Arachidonic Acid

Cyclooxygenase



Prostaglandins
Thromboxanes

5-lipoxygenase



Leukotrienes
C₄, D₄, E₄

Cysteinyl leukotriene receptor

Arachidonic Acid Pathway

Membrane Phospholipids



Phospholipase A₂

Arachidonic Acid

Aspirin
NSAIDs

Cyclooxygenase



Prostaglandins
Thromboxanes

5-lipoxygenase



Leukotrienes
C₄, D₄, E₄

Cysteinyl leukotriene receptor

Leukotriene-Modifying Drugs: Clinical Effects

- Overall, less effective than ICS, but some patients respond well and compliance is higher than for inhalers.
- No good predictors of response: therapeutic trial is needed (over 3-4 weeks).

Role for Leukotriene Modifiers

- Effective in some patients with mild asthma
- Can be combined with inhaled steroids in more severe asthma
- Especially appropriate in aspirin-sensitive asthma
- Few side effects (mood alteration/depression)

Step 3 (Moderate Persistent Asthma)

Equal weight given to two therapeutic options:

- Add LABA to low dose of ICS
- or -
- Increase the dose to ICS to medium-dose range

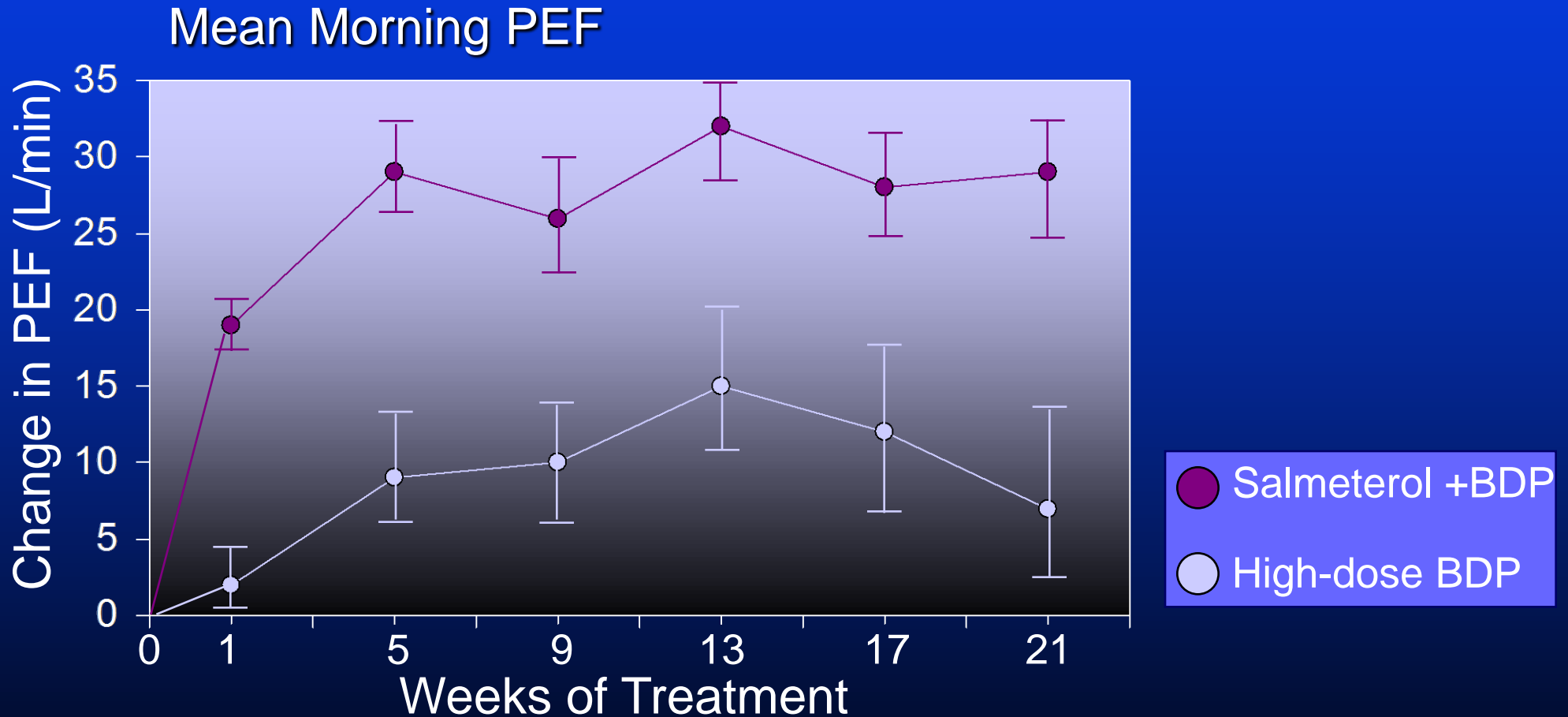
Adding Salmeterol vs. Increasing the Dose of Inhaled Corticosteroids

- 426 patients at 99 general practitioner centers
- Symptomatic despite BDP 400 $\mu\text{g}/\text{day}$
- Randomized to:
 - BDP 400 $\mu\text{g}/\text{day}$ plus salmeterol 50 μg BID*
 - vs. BDP 1000 $\mu\text{g}/\text{day}$*

- Double-blind, double-dummy 6-month trial

Greening et al., *Lancet* 1994;344:219.

Salmeterol in Moderate Asthma: Peak Flow



Safety Concerns Regarding Long-Acting Inhaled Beta-Agonists

Black Box warning regarding salmeterol:

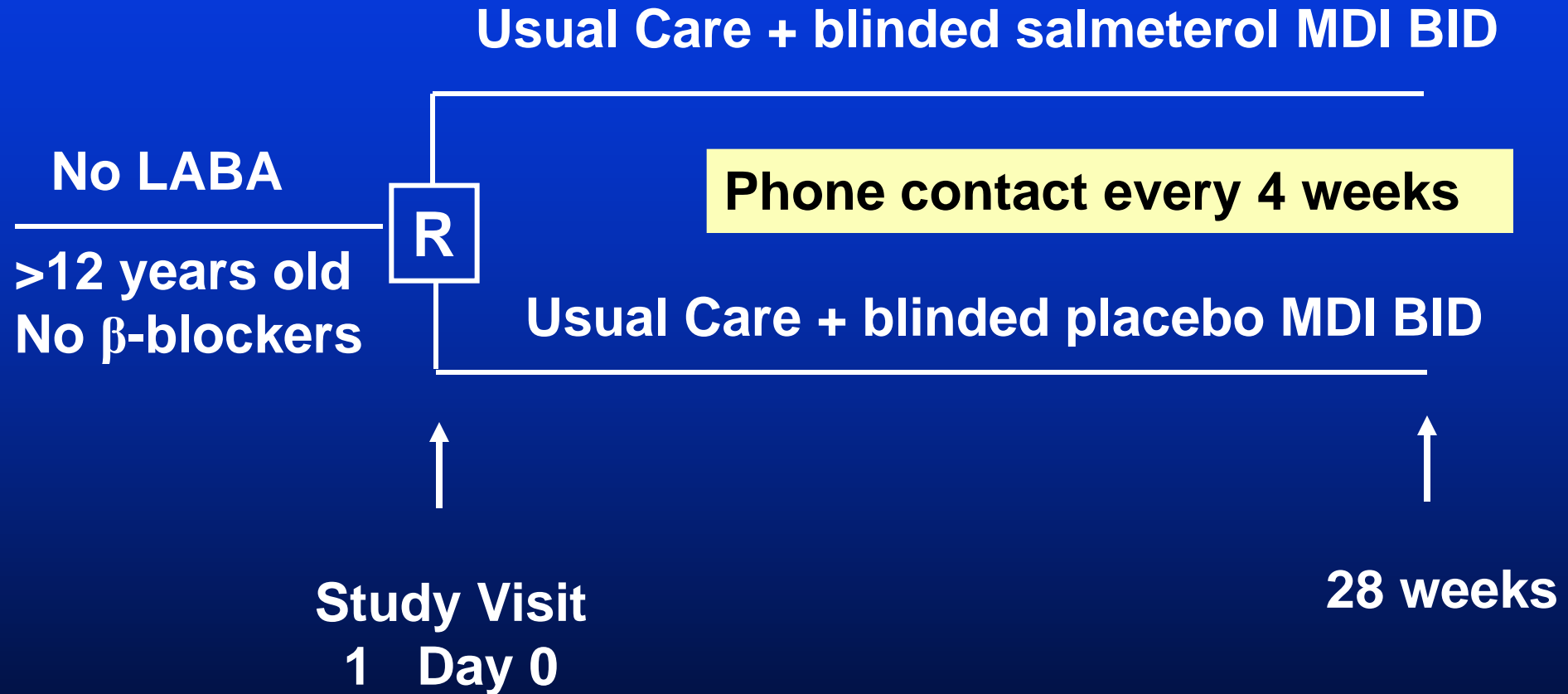
WARNING: DATA FROM A LARGE PLACEBO-CONTROLLED US STUDY THAT COMPARED THE SAFETY OF SALMETEROL (SEREVENT® INHALATION AEROSOL) OR PLACEBO ADDED TO USUAL ASTHMA THERAPY SHOWED A SMALL BUT SIGNIFICANT INCREASE IN ASTHMA-RELATED DEATHS IN PATIENTS RECEIVING SALMETEROL (13 DEATHS OUT OF 13,176 PATIENTS TREATED FOR 28 WEEKS) VERSUS THOSE ON PLACEBO (3 OF 13,179) (SEE WARNINGS AND CLINICAL TRIALS: ASTHMA: SALMETEROL MULTI-CENTER ASTHMA RESEARCH TRIAL).

Salmeterol Multicenter Asthma Research Trial (SMART)

- 26,000 subjects (of planned 60,000) randomized to salmeterol vs placebo plus “usual care” for 6 months
- Outcomes: respiratory/asthma deaths and near-deaths (respiratory failure)

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

SMART: Study Design



Nelson HS, et al., *Chest* 2006; 129:15-26.

Salmeterol Multicenter Asthma Research Trial (SMART)

- Findings at time of study termination:
 - more asthma deaths (13 vs. 3) and more life-threatening or fatal asthma events (37 vs. 22) in the salmeterol-treated group.
- Subgroups at particular risk:
 - African-Americans
 - those not on inhaled steroids

Salmeterol Multicenter Asthma Research Trial (SMART)

	Salmeterol (N=13,176)	Placebo (N=13,179)
Baseline ICS Use	4	3
No Baseline ICS Use	9	0

Salmeterol Multicenter Asthma Research Trial (SMART)

“The data from SMART are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from the risk of serious outcomes.”

-- GlaxoSmithKline in collaboration with the FDA



FDA-Mandated Trials on the Safety of Inhaled LABAs

- 4 placebo-controlled RCTs of ICS + LABA vs. ICS alone in adults (N = 11,700 each) and 1 in children 4-11 years (N = 6,200)
- Primary end point: composite of hospitalization, intubation, and asthma-related deaths
- 90% power to detect doubling of relative risk
- Begun in 2011, results in 2017

Chowdhury BS, et al, *NEJM* 2011; 364:2473.

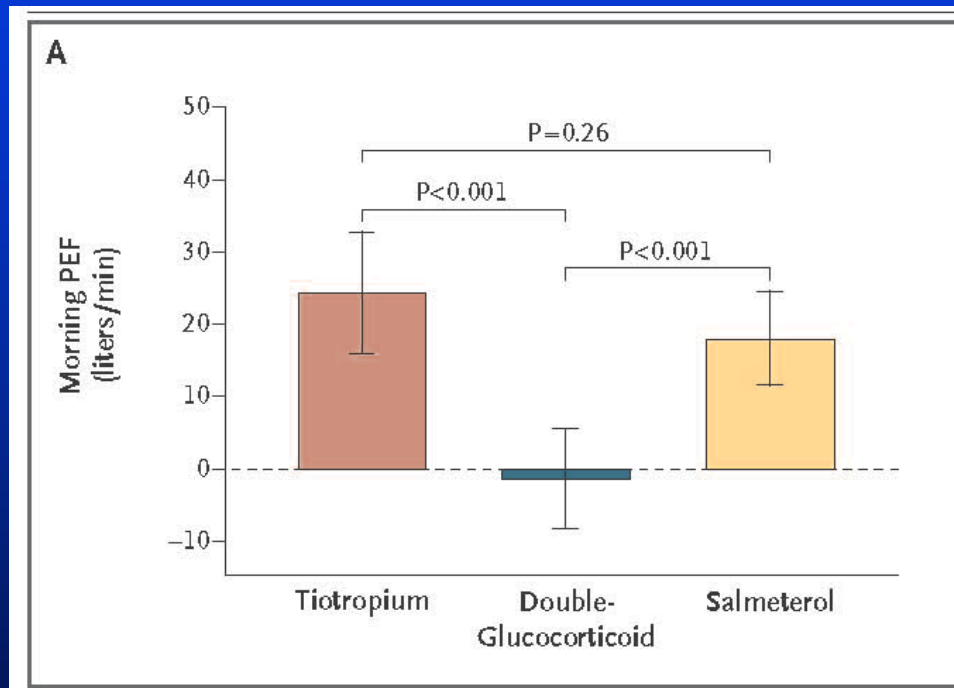


Alternative Long-Acting BD: Anti-Cholinergic (Tiotropium)

- 210 subjects with asthma poorly controlled on beclomethasone 160 mcg/day
- Randomly assigned to:
 - Beclomethasone 320 mcg/day
 - Beclo 160 mcg/day + Salmeterol BID
 - Beclo 160 mcg/day + Tiotropium qD

Peters SP, et al (ACRN). *NEJM* 2010; 363:1715-26.

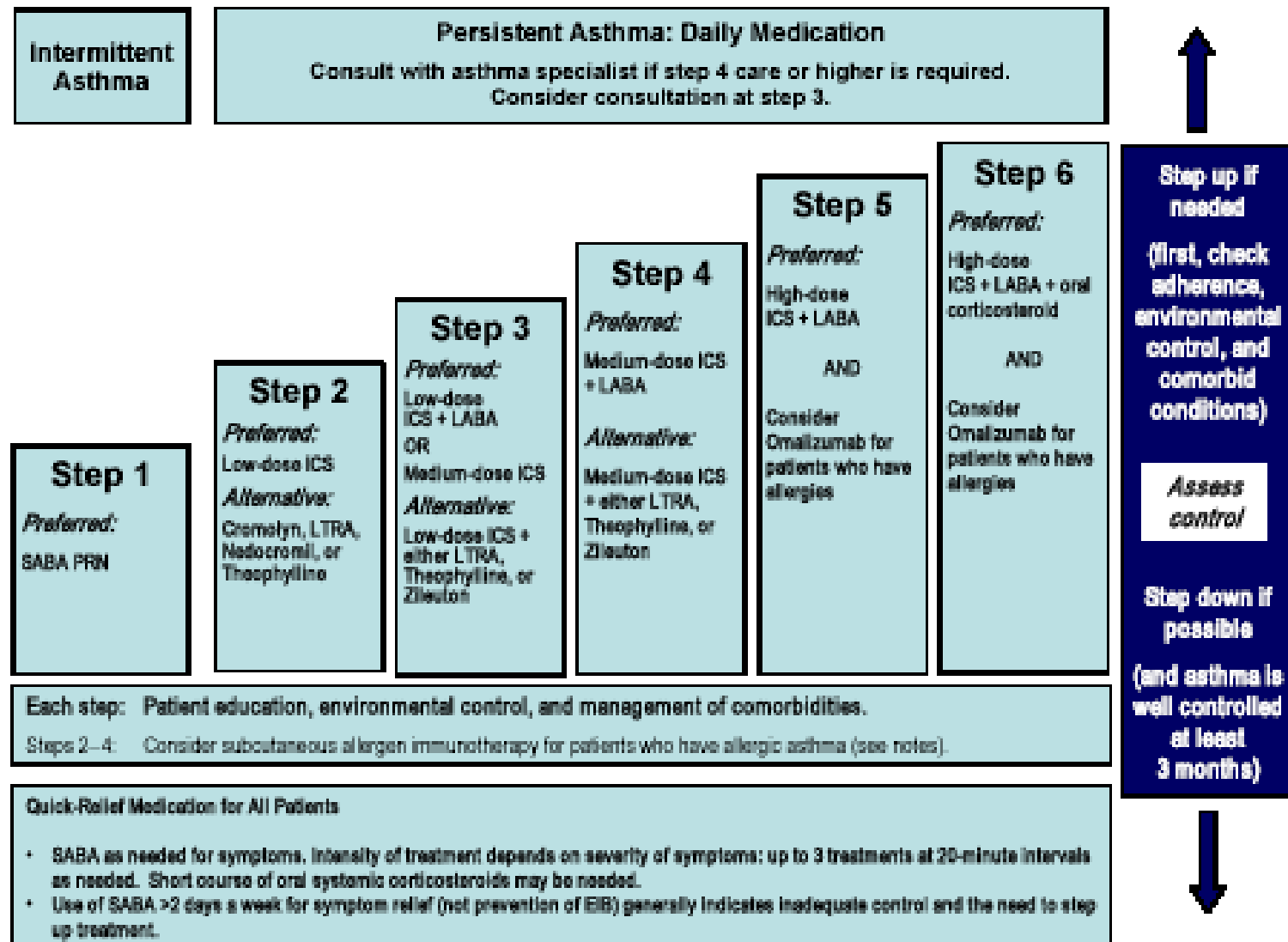
ICS + Tiotropium in Asthma (TALC)



Adding tiotropium to ICS was **non-inferior** to adding salmeterol in all outcomes measured.

Peters SP, et al (ACRN). *NEJM* 2010; 363:1715-26.

FIGURE 4-5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS



Combination ICS and Long-Acting Bronchodilators

Combination inhalers:

- Fluticasone + salmeterol (Advair)
 - MDI 45/21, 115/21, 230/21
 - DPI 100/50, 250/50, 500/50
- Budesonide + formoterol (Symbicort)
 - MDI 80/4.5, 160/4.5
- Mometasone + formoterol (Dulera)
 - MDI 100/5, 200/5

... or once-daily ICS/LABA

- Ultra-long-acting beta-agonist bronchodilator plus once-daily inhaled corticosteroid:

vilanterol + fluticasone furoate
(Breo Ellipta)



“Stepping Down” Asthma Therapy

Once good asthma control is achieved, attempt to :

- stop the long-acting beta-agonist bronchodilator;
- reduce the dose of inhaled corticosteroids

to minimize the potential risk for severe asthmatic attacks and long-term side effects.

Achieving Asthma Control

The Five-Point Plan:

- A. Making the correct diagnosis
- B. Modifying environmental inciters
- C. Medications to control asthma
- D. *Plan for dealing with asthmatic attacks***
- E. Specialist consultation

Key Components of an Asthma Action Plan

Teach your patients to:

- Recognize when they are having an asthma attack;
- Assess the severity of the attack;
- Have a plan to respond to the attack; and
- Know when and how to get help.

Key Components of an Asthma Action Plan

- ... and put it in writing!

Traffic-Light Model: Green-Yellow-Red Zones

- **Green zone:** PEFr 80 – 100%
- **Yellow zone:** PEFr 50 – 80%
- **Red zone:** PEFr <50%



General Strategies

- Use your quick-relief bronchodilator more frequently than usual
- Increase your dose of inhaled steroids
- For severe attack, begin or increase dose of oral steroids

Managing Asthmatic Attacks

- Frequent inhaled bronchodilators (albuterol +/- ipratropium)
 - - by nebulizer or MDI with spacer
- Oral corticosteroids (prednisone 40-60 mg/day)
 - - oral = i.v.
 - - no taper necessary
 - - duration? – until lung function close to baseline
 - - continue inhaled steroids thereafter

Achieving Asthma Control

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Indications for Specialist Consultation

- Uncertainty regarding diagnosis;
- Failure to achieve good asthma control;
- Frequent need for systemic steroids;
- Frequent ED visits or hospitalizations;
- Unacceptable medication side-effects.

Evaluation of Difficult-to-Control Asthma: Systematic Approach

- Inciting agents
- Aggravating conditions
- Medication non-compliance
- Alternative diagnoses

Case Example

A 43 year-old woman was referred for management of her severe, steroid-dependent asthma.

She had suffered asthma since childhood. In the past several years, she had taken prednisone on a nearly daily basis. On the day of her office visit, despite taking prednisone 30 mg/d, she had loud wheezing audible across the examination room.

Case Example (cont.)

In the past few years, she had been intubated at least twice for her asthma.

She had multiple steroid-induced complications of her therapy, including weight gain, mood facies, striae, ecchymoses, and cataracts.

Case Example (cont.)

Her past history was remarkable for a psychiatric disorder, treated with major tranquilizers.

Her examination revealed loud expiratory wheezes best heard without a stethoscope. Her expiratory wheezes sounded somewhat distant on auscultation of the chest.

Case Example (cont.)

Medical records were subsequently available from one of her ED visits prior to intubation and mechanical ventilation:

She was described as being in respiratory distress with loud wheezing. Her arterial blood gases were as follows:

PO₂ 98 mm Hg, PCO₂ 29 mm Hg, pH 7.47

Case Example (cont.)

Despite intensive treatment with inhaled bronchodilators and intravenous corticosteroids in the emergency department, she appeared to “tire.” Repeat arterial blood gases were:

PO₂ 102 mm Hg, PCO₂ 24 mm Hg, pH 7.52, and she was intubated.

Vocal Cord Dysfunction Syndrome

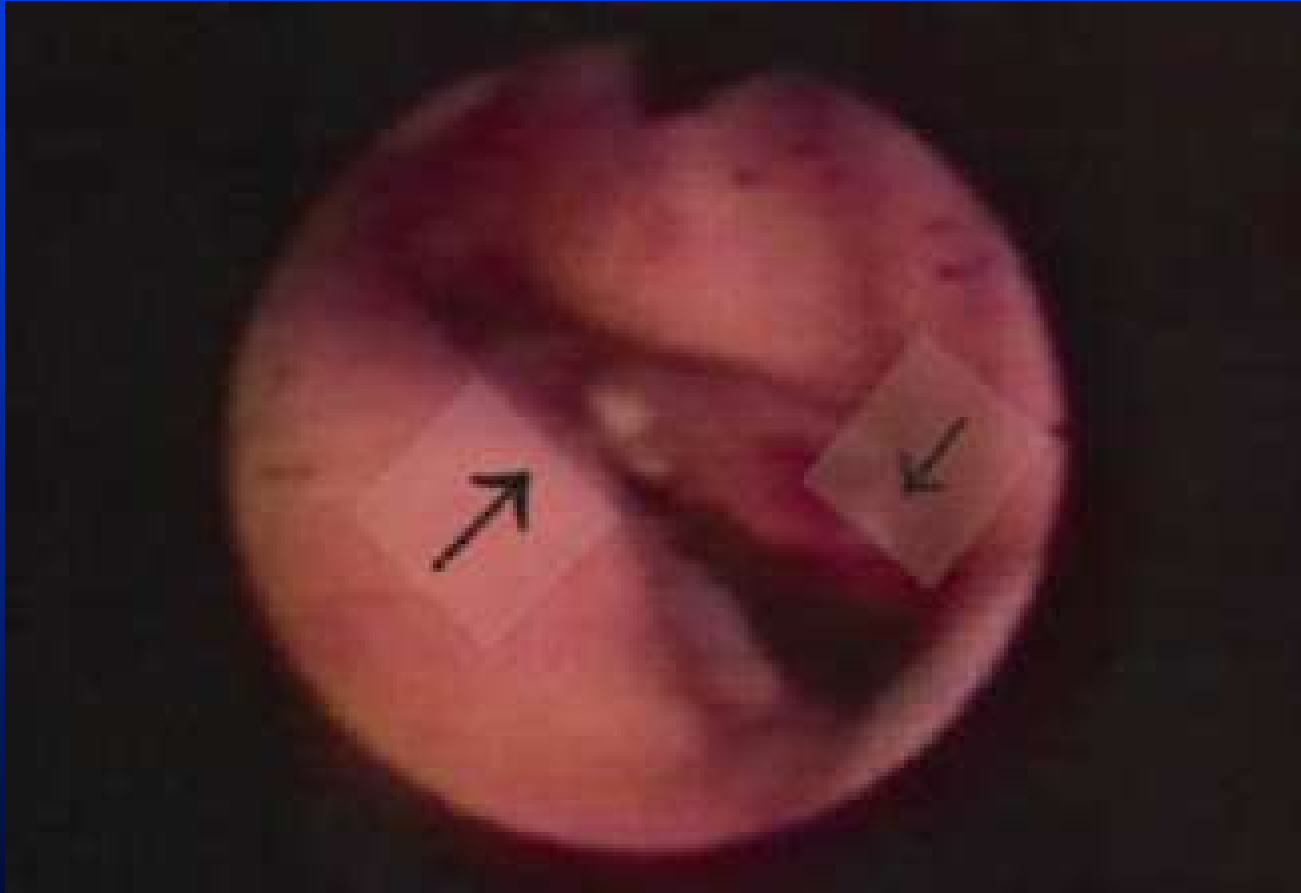
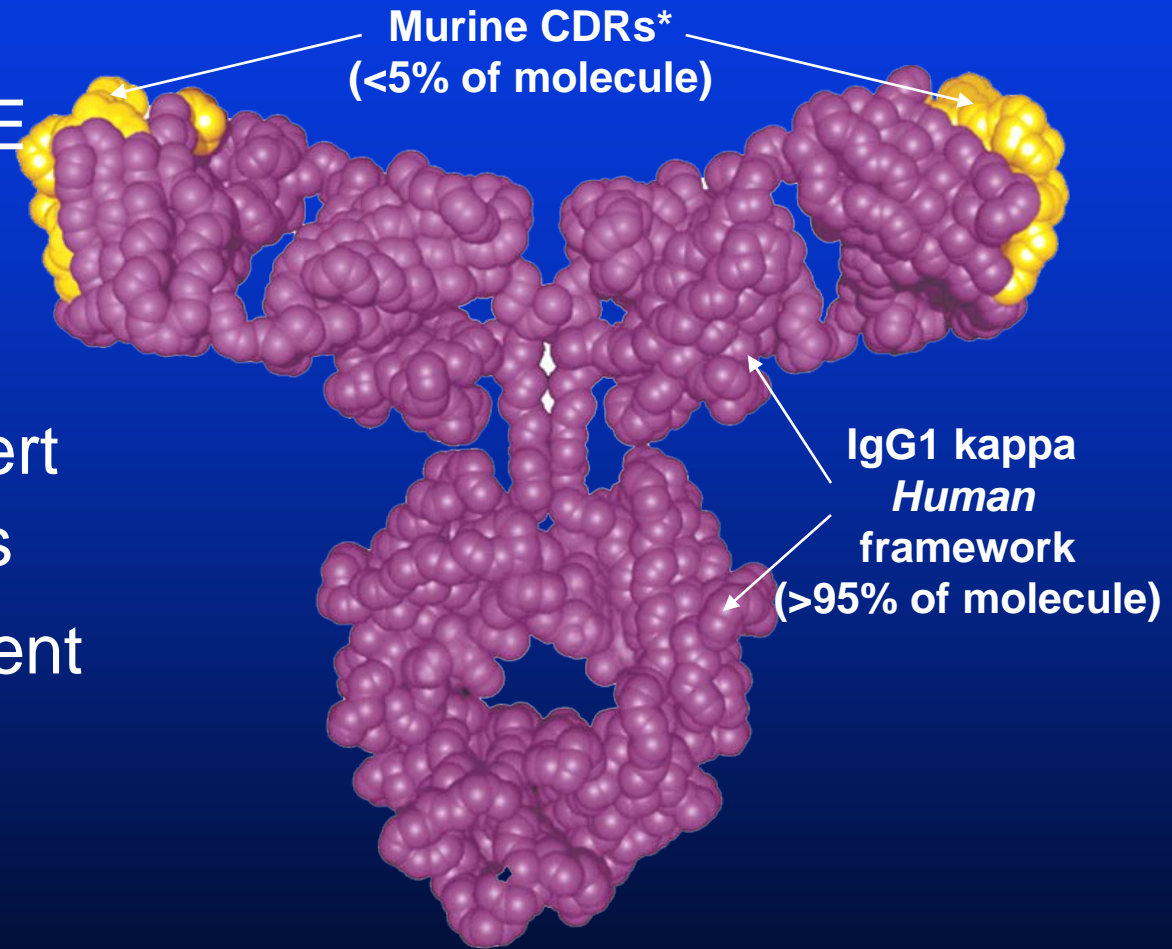


Image from
www.emedmag.com

Omalizumab Characteristics

- Humanized mAb against IgE
- Binds circulating IgE regardless of specificity
- Forms small, biologically inert Omalizumab:IgE complexes
- Does not activate complement



*CDR = complementarity-determining region

Adapted with permission from Boushey H. *J Allergy Clin Immunol.* 2001;108:S77-S83.

Omalizumab: Study Outcomes

Efficacy:

- Fewer, shorter asthmatic exacerbations
- Reduced steroid doses
- Less need for bronchodilator
- Improved lung function and symptom scores

Adverse effects:

- Anaphylactic reactions (1:1000)
- ??Increased risk of neoplasm
- ??Increased incidence of cardiovascular events

Busse W, et al., *JACI* 2001; 108:184.

Solèr M, et al., *Eur Respir J* 2001; 18:254-61.

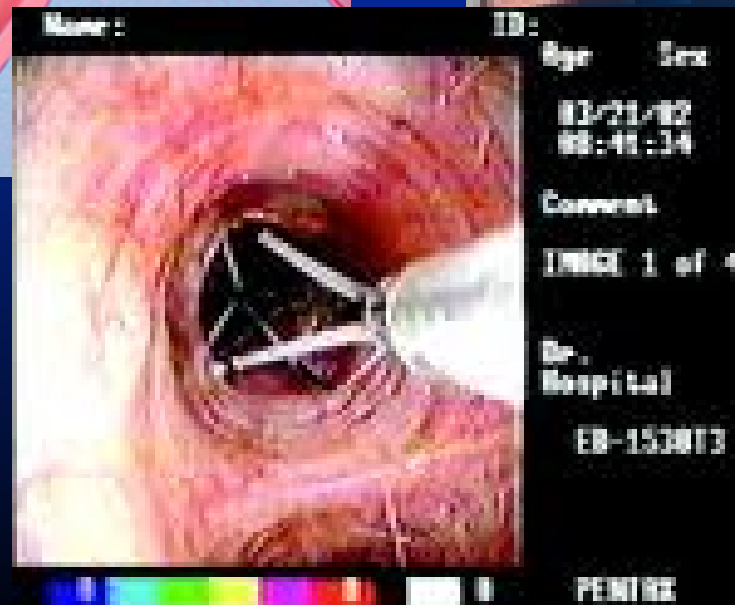
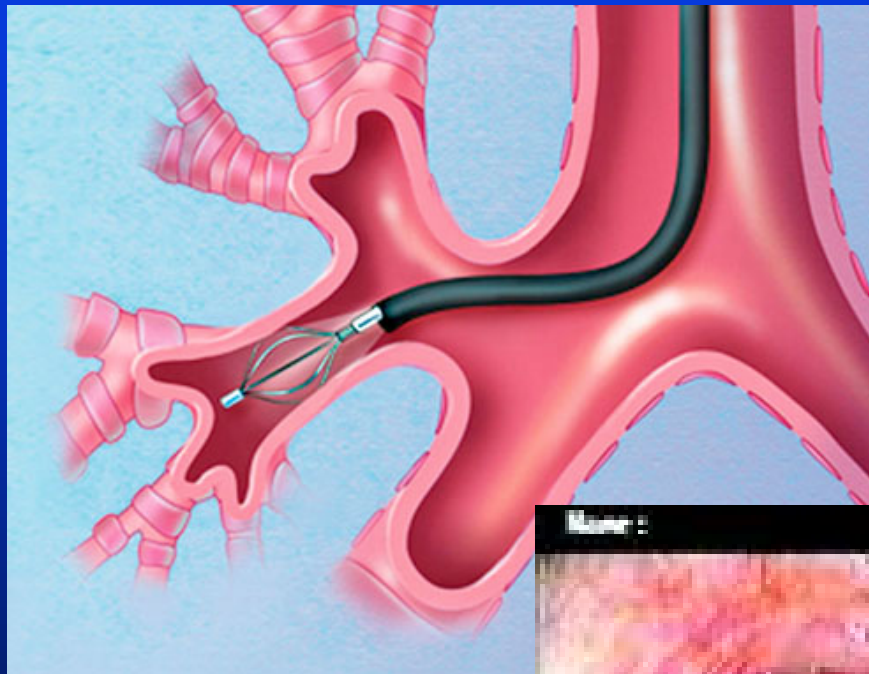
Anti-IgE Monoclonal Antibody: Omalizumab (Xolair)

Indications: Severe, atopic asthma:
total serum IgE 30 – 700 IU/ml;
sensitivity to ≥ 1 perennial antigen.

Benefits: Dominant effect: fewer exacerbations

Negatives: Cost; small risk of anaphylaxis;
injections given every 2-4 weeks
indefinitely.

Bronchial Thermoplasty



Bronchial Thermoplasty

Efficacy:

- Improved AQLQ score
- Fewer asthmatic exacerbations
- Fewer ED visits
- Fewer days missed work/school

No significant differences:

- Morning PEF
- Symptom-free days
- Rescue medication use
- Symptom score or ACQ

Bronchial Thermoplasty

Adverse events:

- Hospitalization for respiratory symptoms (8.4%)
- Worsening asthma
- Segmental atelectasis
- Lower RTI
- Hemoptysis (treated with bronchial artery embolization)
- Aspirated tooth

Castro M, et al., *AJRCCM* 2010; 181:116.

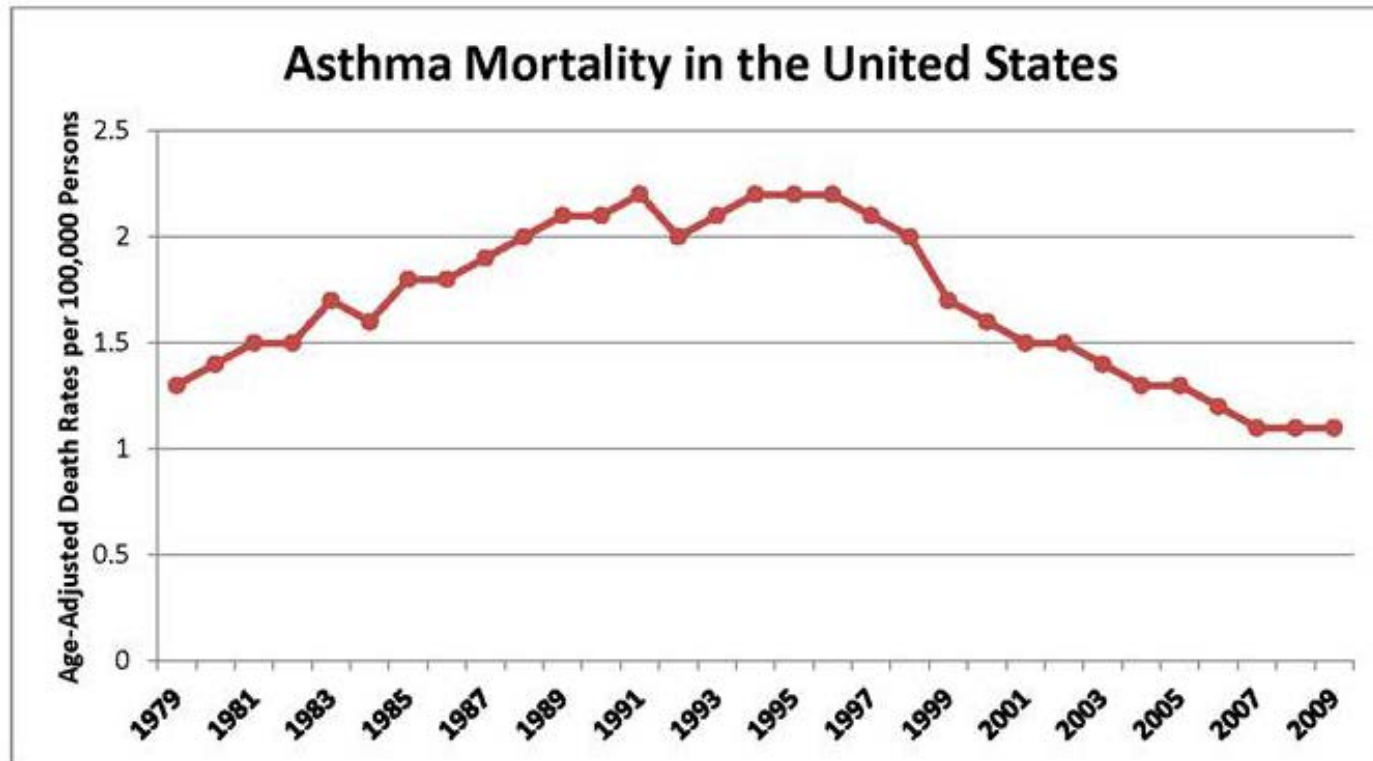
Bronchial Thermoplasty

Procedure: 3 bronchoscopies over 6 weeks

Benefits: Improved quality of life;
fewer exacerbations

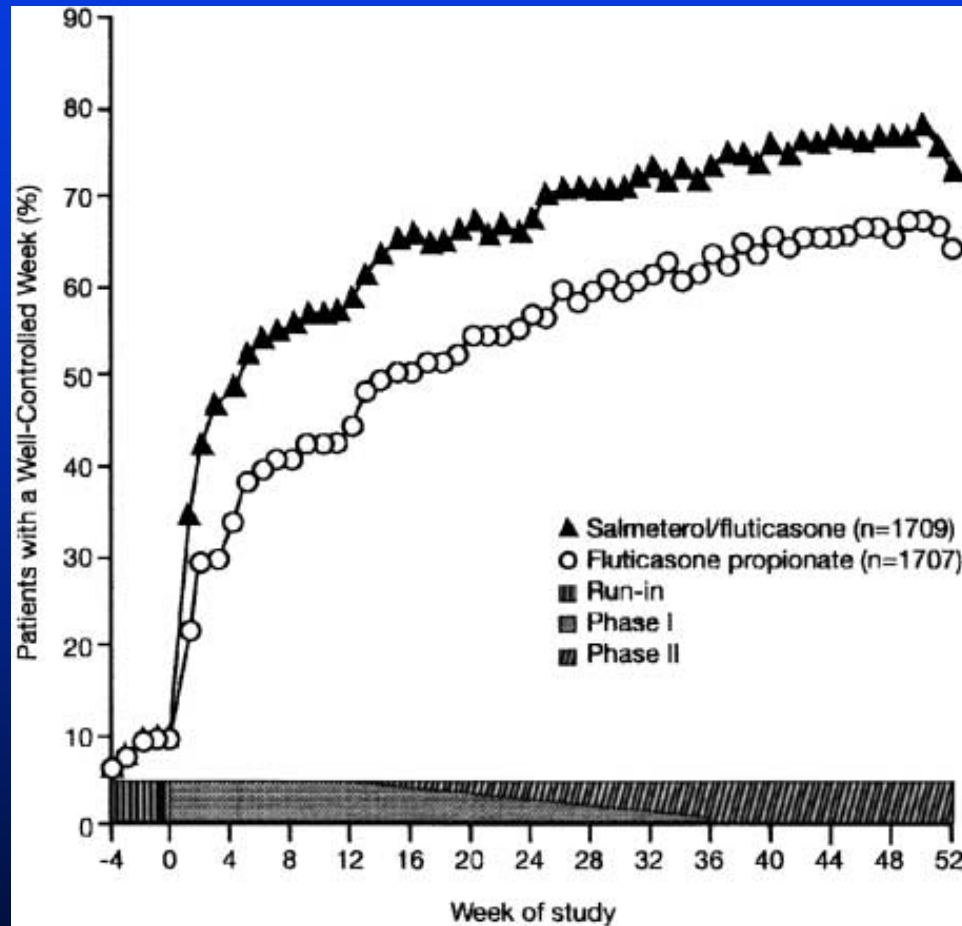
Risks: Bronchoscopy-associated
asthmatic exacerbations,
complications; ?long-term sequelae

Trends in Asthma Deaths in U.S.



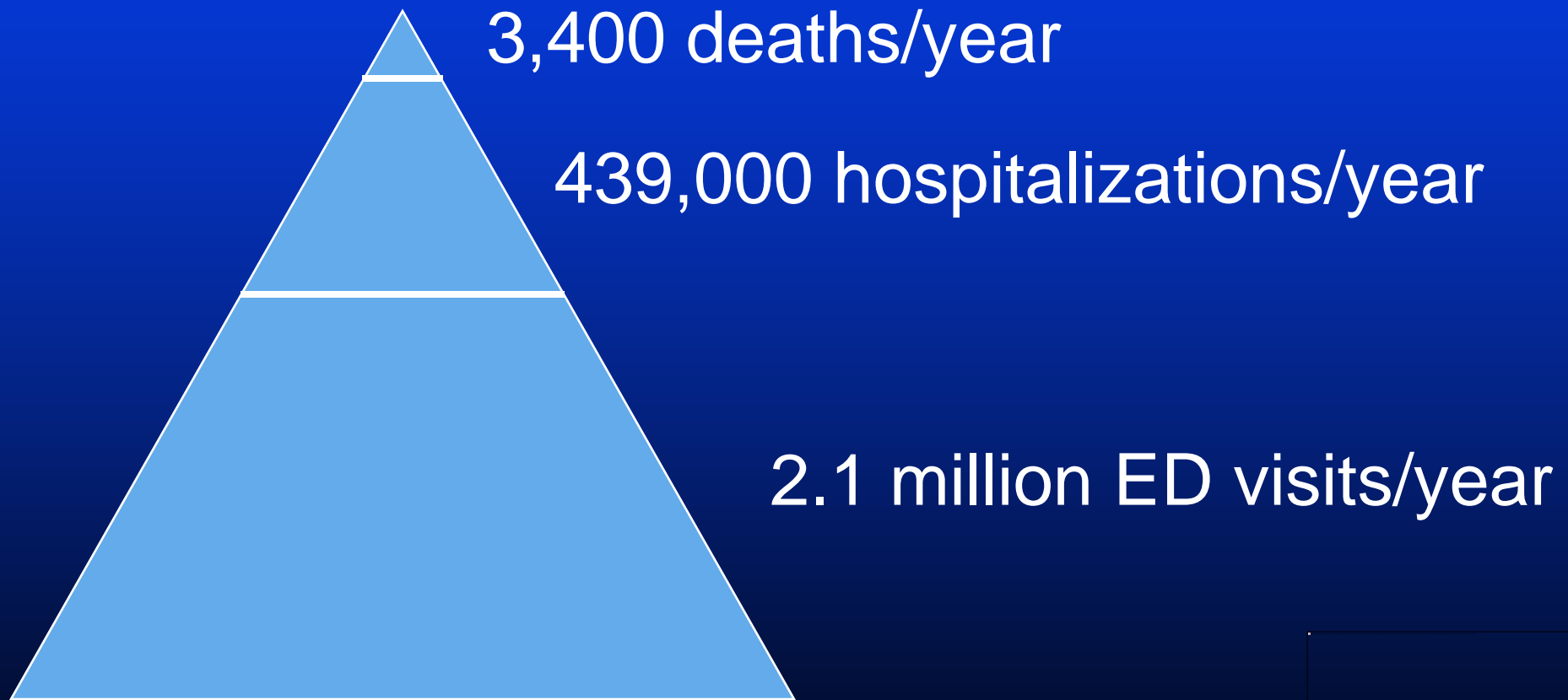
**Trends in
Asthma
Statistics,
Feb. 2010.
American
Lung
Association**

Gaining Optimal Asthma Control (GOAL)

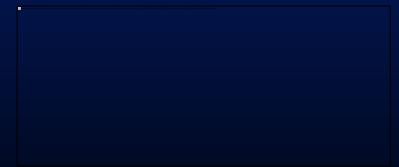


Bateman BD, et al. *Am J Respir Crit Care Med* 2004; 170:836-44.

Epidemiology of Asthmatic Attacks



Asthma Fact Sheet, 2012
American Lung Association (data for 2009)



Partners Asthma Center

Thank you.

www.asthma.partners.org

www.asthmalearning.org

www.pacasthma.blogspot.com

