Asthma 2013: Clinical Highlights and Controversies

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Disclosures/Conflict of Interest

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Speakers Bureau: None

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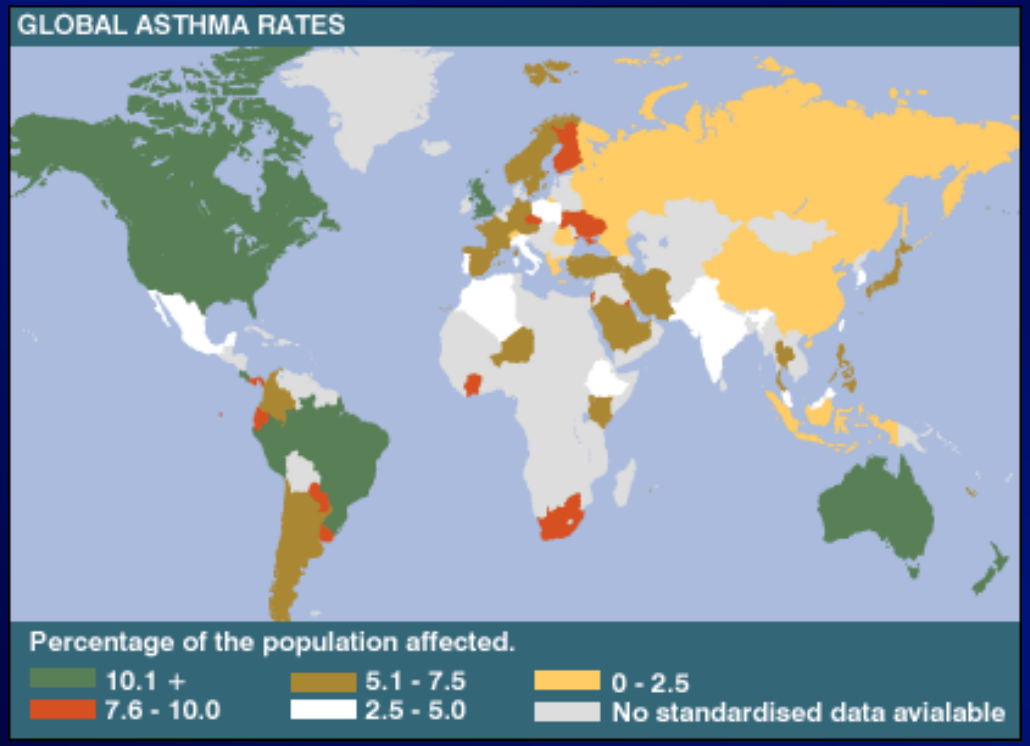
Trends of Asthma Morbidity/ Mortality

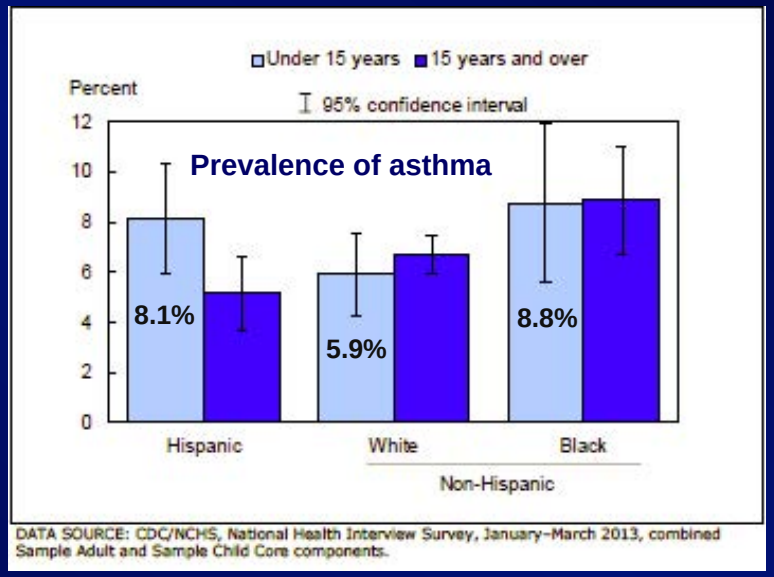


Asthma: more common in developed countries
Exacerbations more common in:
- Minority populations
- Lower socio-economic groups

Asthma Facts: Each Day

- 44,000 asthma attacks
- 4,700 visit E.D. with asthma
- 1,200 admitted to a hospital
- 9 people die from asthma

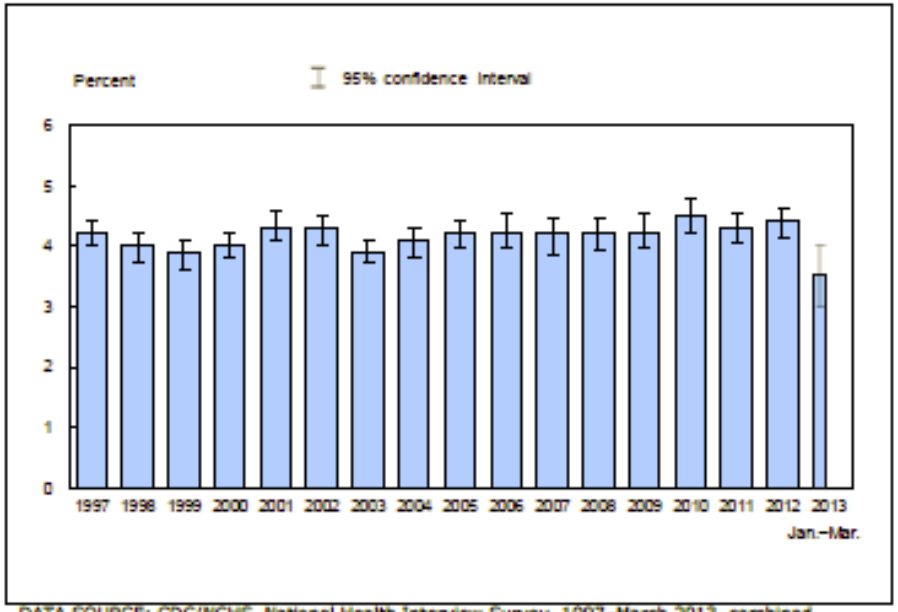
Racial Disparity in U.S.



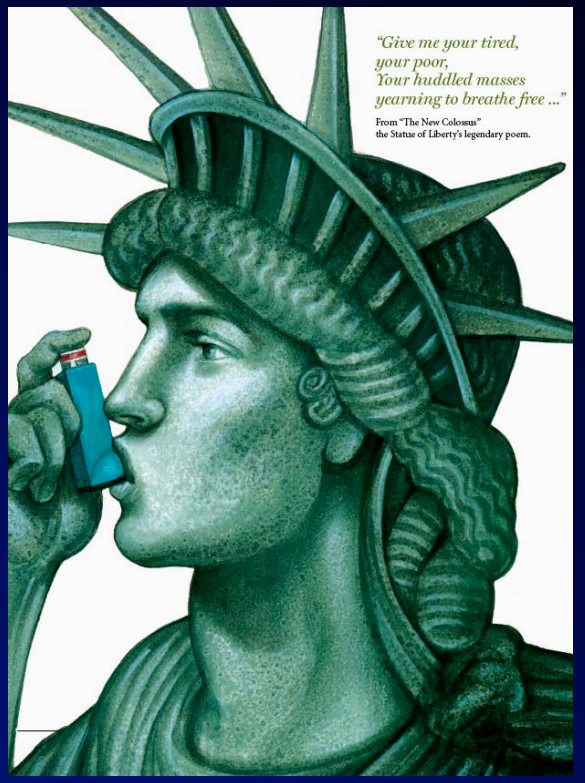
Asthma Trends: CDC posting May 2013

Time to be optimistic?

Figure 15.1. Percentage of persons of all ages who experienced an asthma episode in the past 12 months: United States, 1997–March 2013



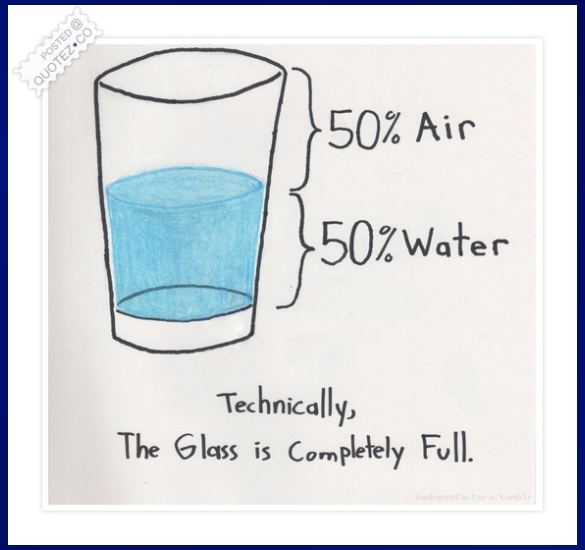
DATA SOURCE: CDC/NCHS, National Health Interview Survey, 1997–March 2013, combined Sample Adult and Sample Child Core components.



National Health Interview Survey (NHIS)

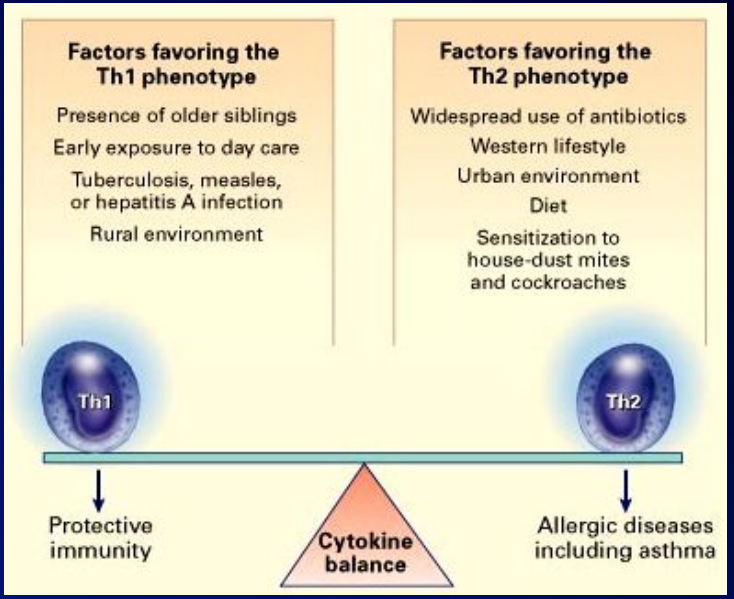
- **Prevalence of current asthma increased: 2003 vs. 2012 = 7.1% vs. 8.5 %**
- **Percentage with exacerbation fell 8.5% to 6.8%**

Still 3,285 unnecessary asthma deaths!

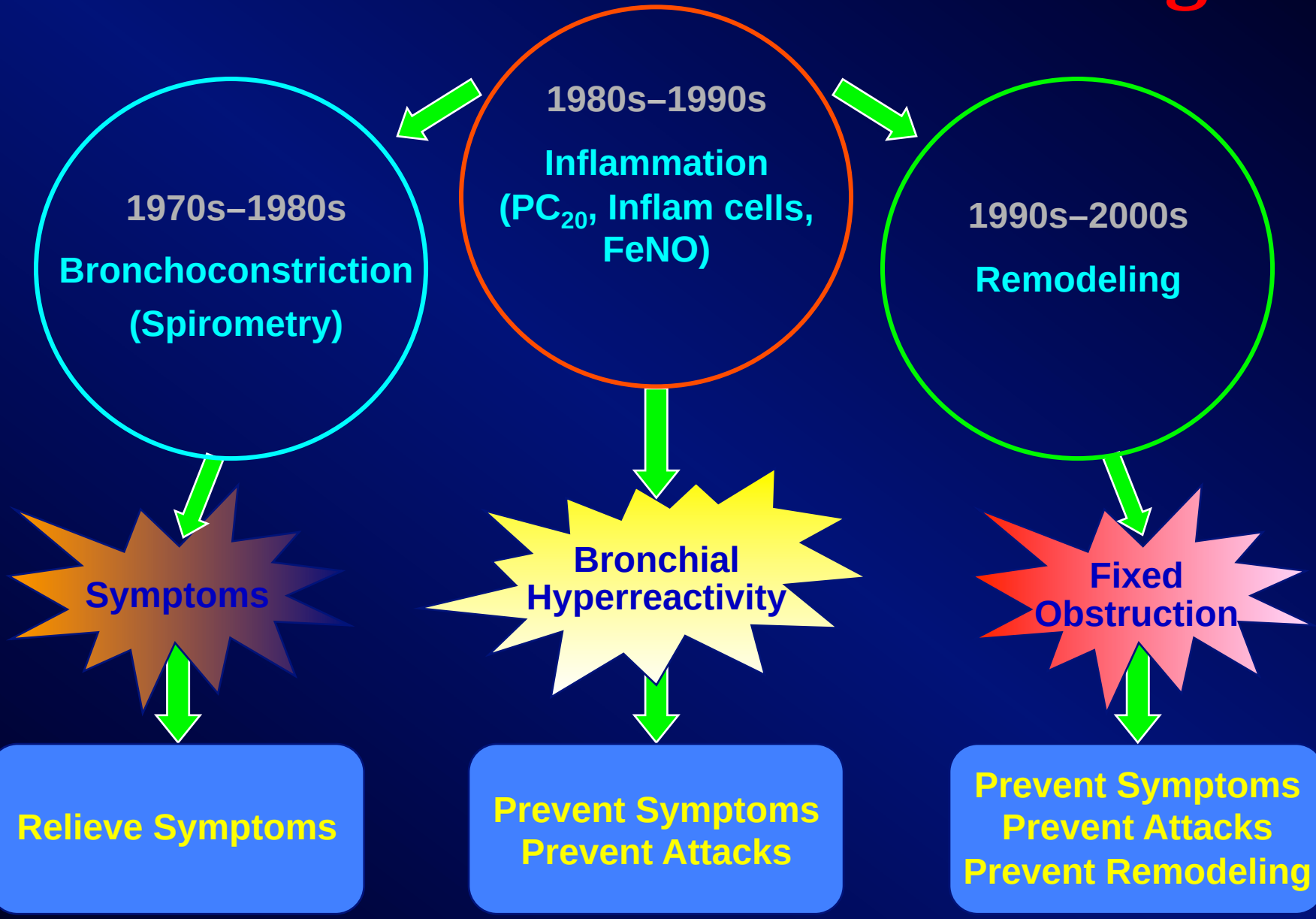


Asthma is a Complex Disease

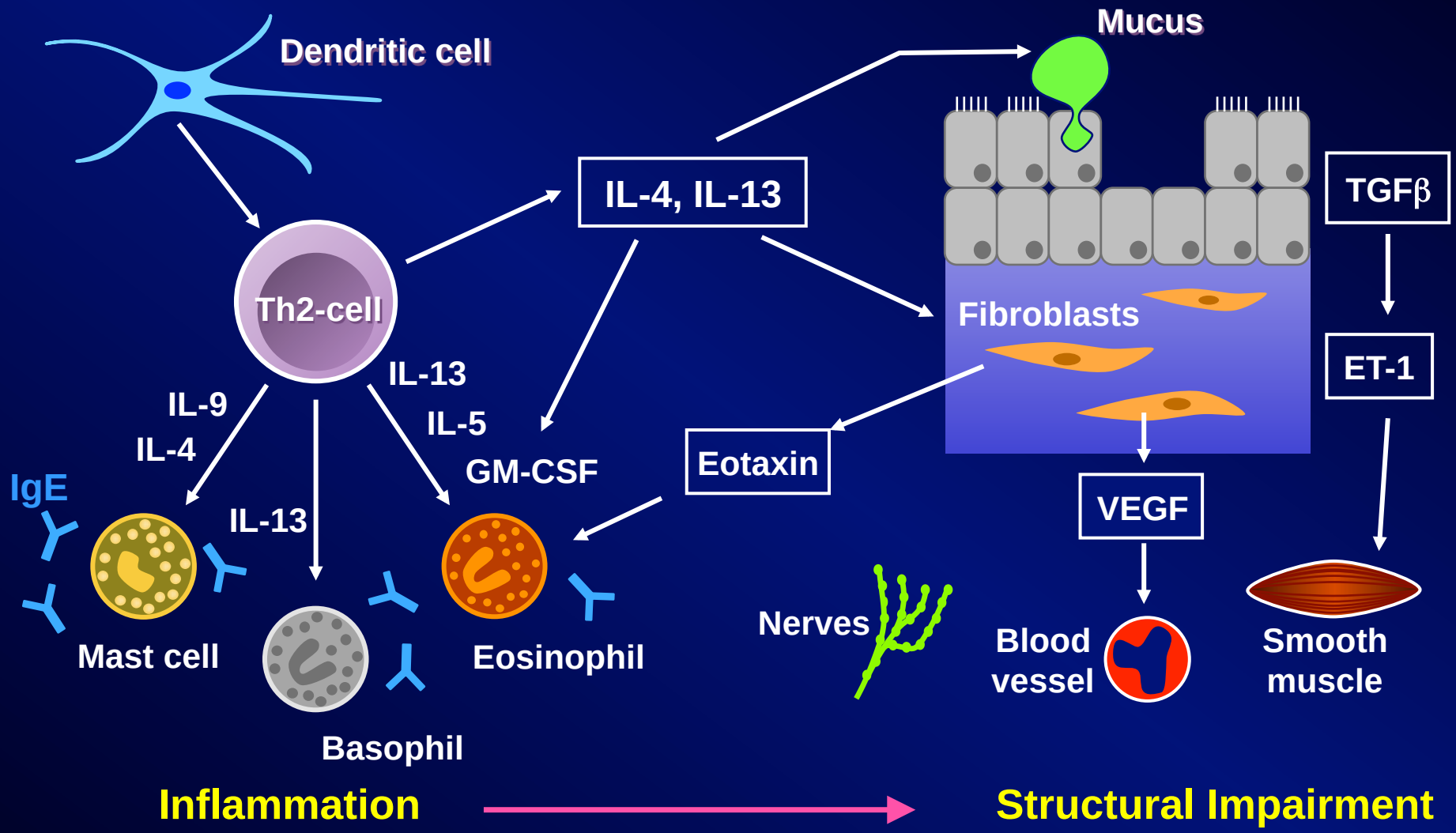
- **Genetics of asthma**
  - One parent: risk 1/3
  - Both parents: risk 7/10
  - Identical twin: only 50-70%
- Environment & asthma
  - Increased risk: western lifestyles, use of antibiotics and vaccines, allergen exposure
  - Decreased risk: large number of siblings, rural environment
- Timing: early vs. late exposure (e.g. cats, infection)



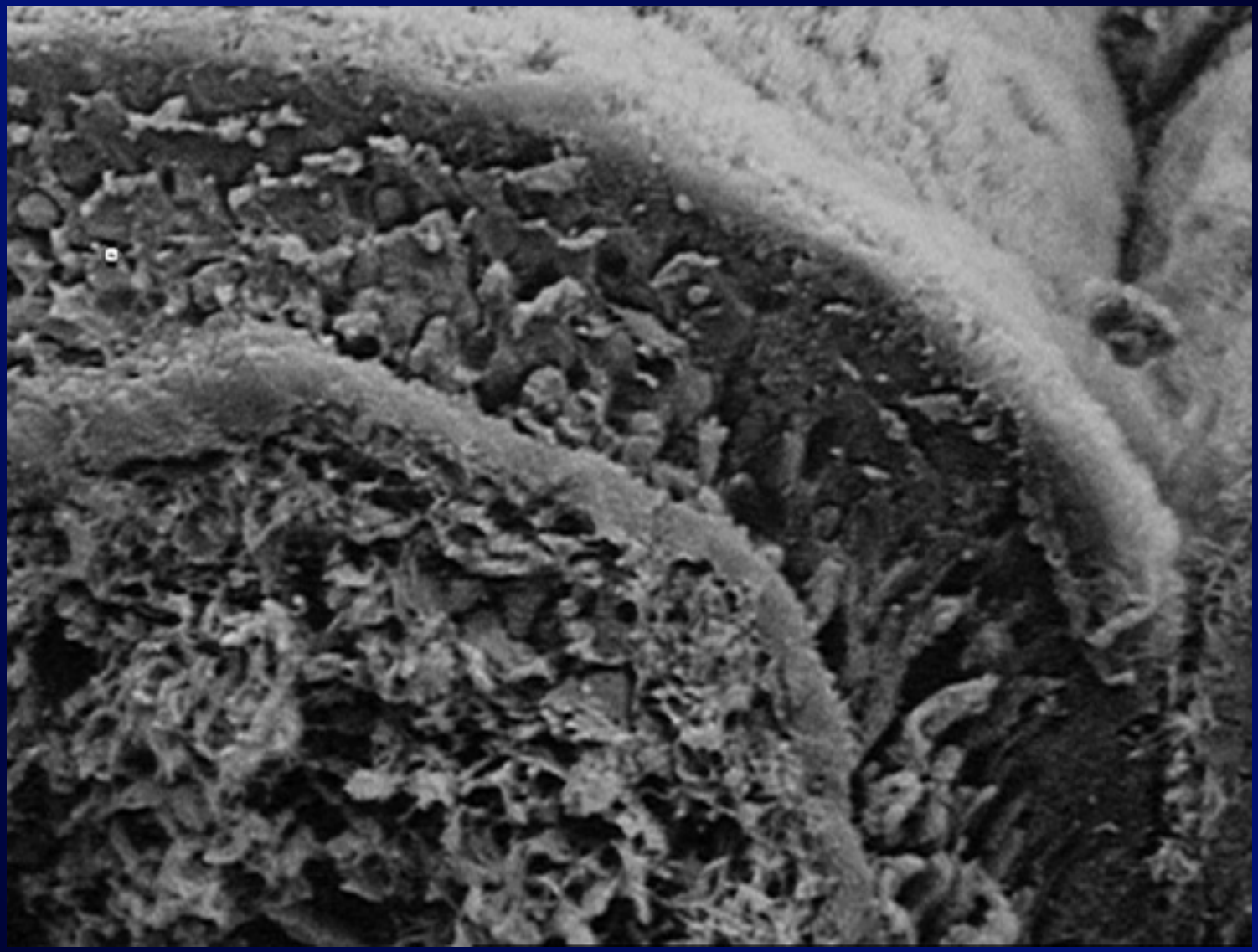
Evolution of Asthma Paradigms



The Airway Microenvironment in Asthma

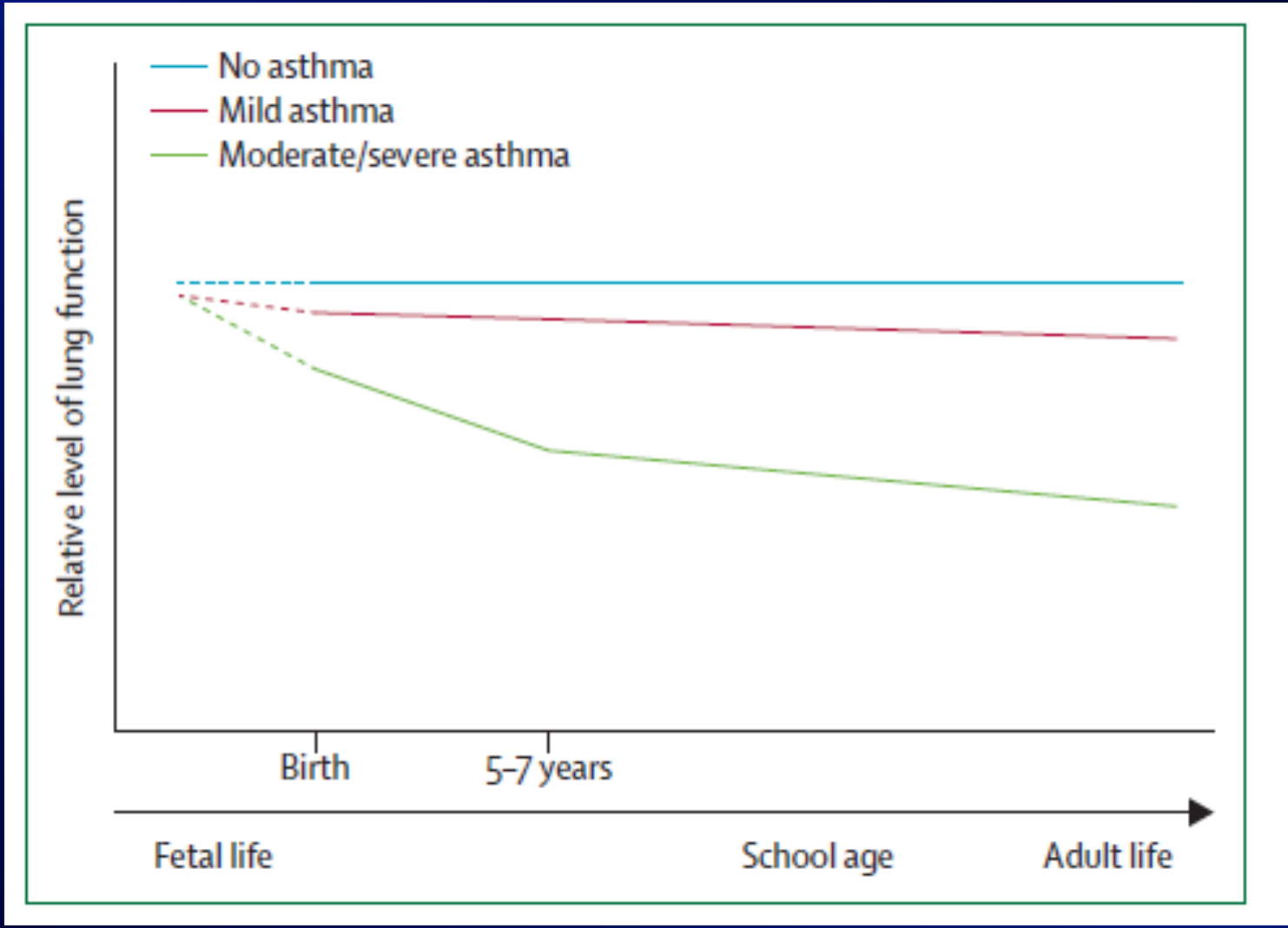


Basement Membrane Thickening



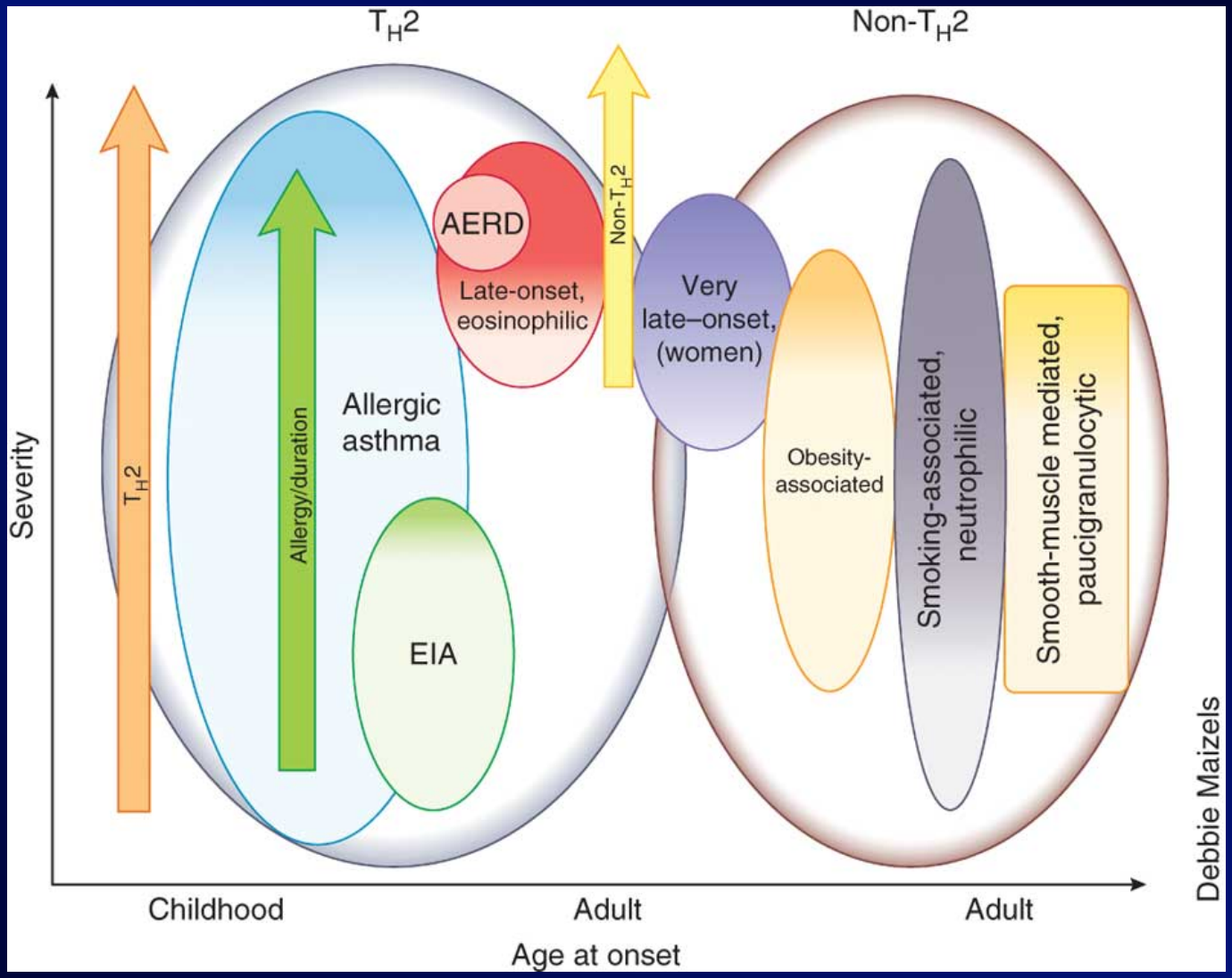
Jeffery P. In: Asthma, Academic Press 1998.

Changes in Lung Function in Asthma



Martinez F, Vercelli D. *Lancet* 2013

Clinical Asthma Phenotypes



Wenzel S. *Nature Med* 2012; 18:716-25

Asthma Phenotypes

- Early onset asthma: ≤ 12 yrs old
  - Atopic (elevated IgE levels): skin, nasal, & lung involvement
  - Eosinophilic inflammation; allergy driven/responsive
- Adult onset asthma: > 18 yrs old (mean 54; range 26-75)
  - Group 1: Eos $^{+}$; persistent airflow obstruction; low Sx score
  - Group 2: Obese females, low Eos, high Sx score/health costs
  - Group 3: Mild-moderate asthma, nl lung function and low inflammatory markers
- Severe asthma phenotype
  - Disease moves more distal in airways
  - Neutrophils and mast cells in terminal airways

Allergy 68 (5),674-80 (May 2013)

The Asthma Syndrome

Symptoms of asthma, episodic breathlessness, wheeze, cough

Asthma Endotypes

Distinct disease entities which may be present in clusters of phenotypes and each having a specific biological mechanism

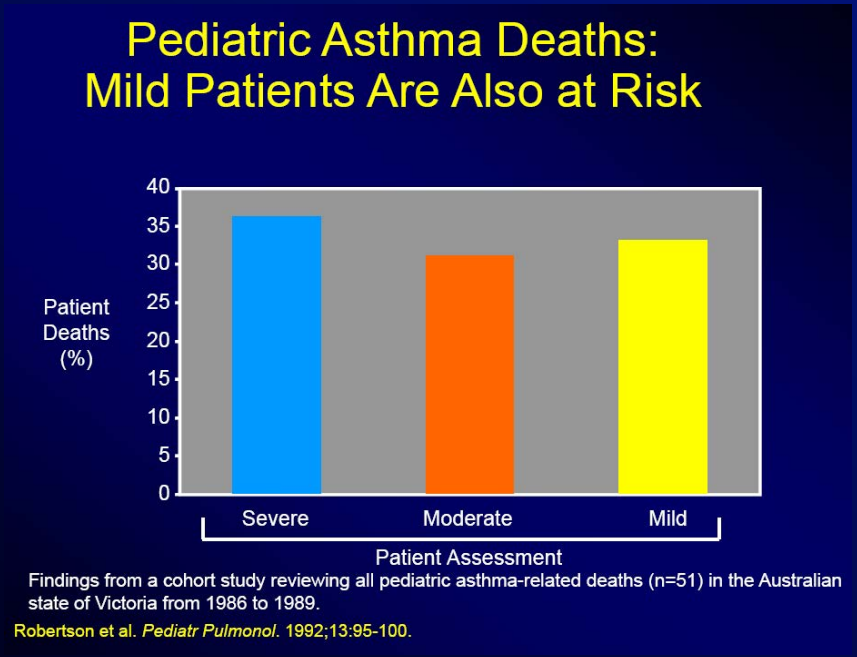
Endotype 1 Allergen driven	Endotype 2 Severe eosinophilic non-allergic	Endotype 3 Non-eosinophilic	Endotype 4 Non-inflammatory	Endotypes not yet identified or rare

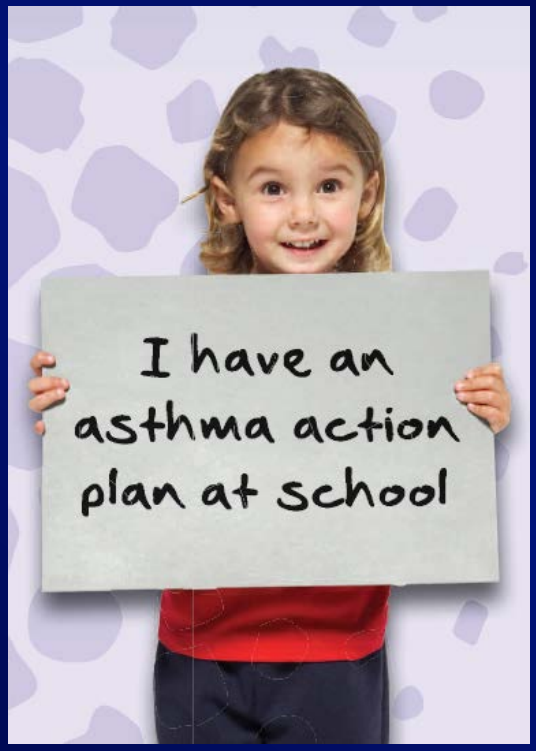
Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome

Jan Lötvall, MD,[a] Cezmi A. Akdis, MD,[b] Leonard B. Bacharier, MD,[c] Leif Bjermer, MD,[d] Thomas B. Casale, MD,[e] Adnan Custovic, MD,[f] Robert F. Lemanske, Jr, MD,[g] Andrew J. Wardlaw, MD,[h] Sally E. Wenzel, MD,[i] and Paul A. Greenberger, MD[j] *Göteborg and Lund, Sweden, Davos, Switzerland, St Louis, Mo, Omaha, Neb, Manchester and Leicester, United Kingdom, Madison, Wis, Pittsburgh, Pa, and Chicago, Ill*

#1 Cause of Asthma Deaths

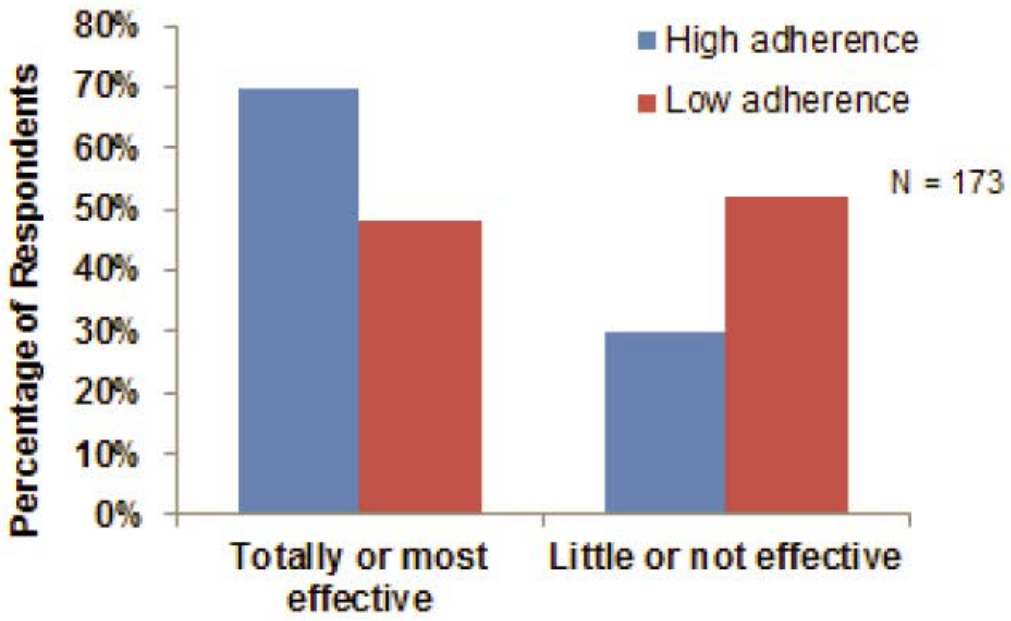
- **Noncompliance**
  - **Lack of asthma education (both patients/MDs)**
  - **Failure to prescribe/use controller medications**
- **Belief that asthma deaths only occur in patients with severe asthma**





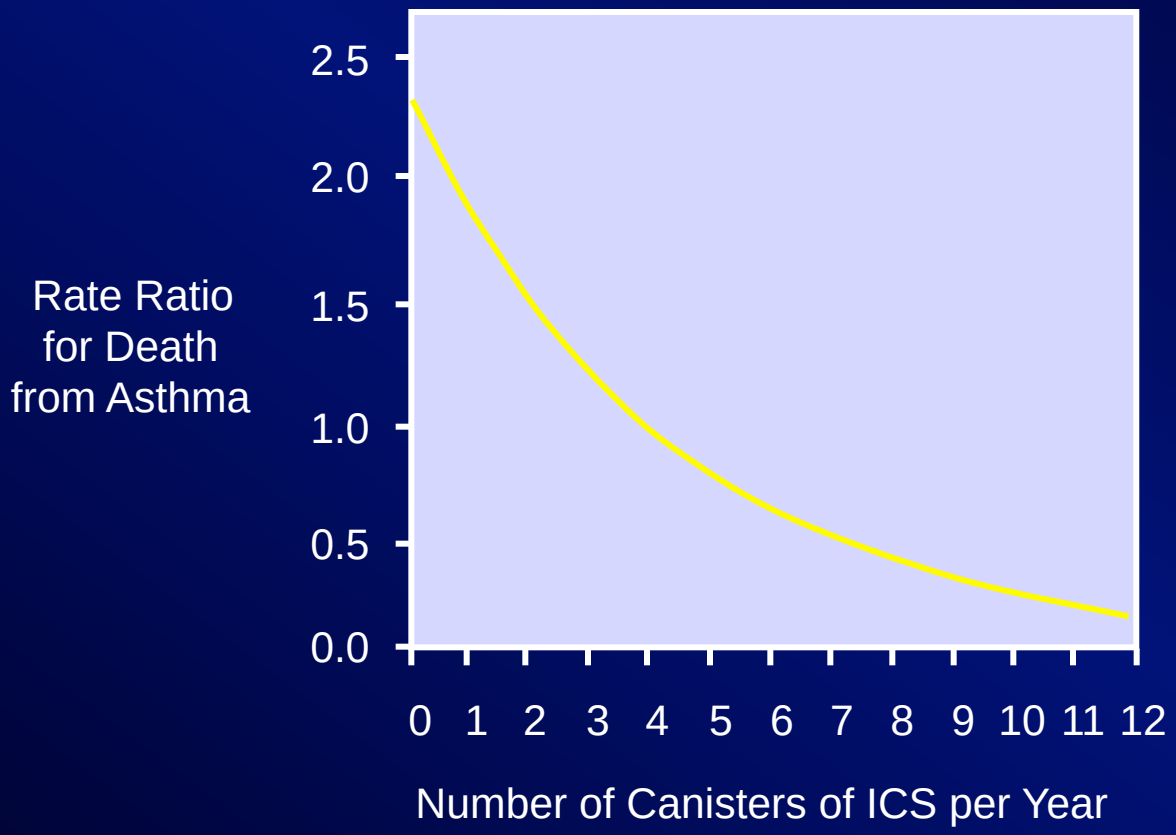
Patient Education/Beliefs Can Prevent Asthma Deaths

Patient-related Factors: Belief in Treatment Efficacy Is Associated With Higher Adherence



Khdour MR, et al. *Eur J Clin Pharmacol.* 2012;68(10):1365-1373.

Low-dose ICS: Prevention of Death from Asthma

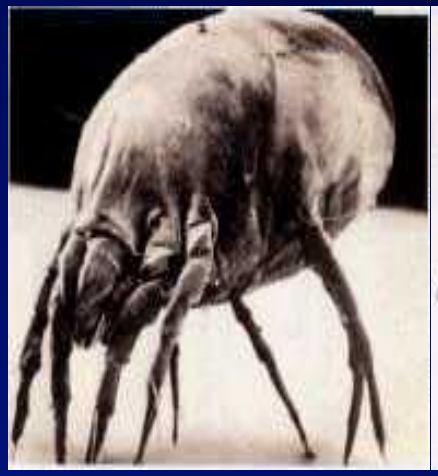


Suissa et al. *N Engl J Med.* 2000;343:332-336.

Education About the Environment

- **Allergens avoidance in asthma:**
  - **House dust mite**
  - **Cat dander**
  - **Cockroach antigen**
  - **Alterneria/fungi**

- **Most forgotten component in asthma education**



Mites

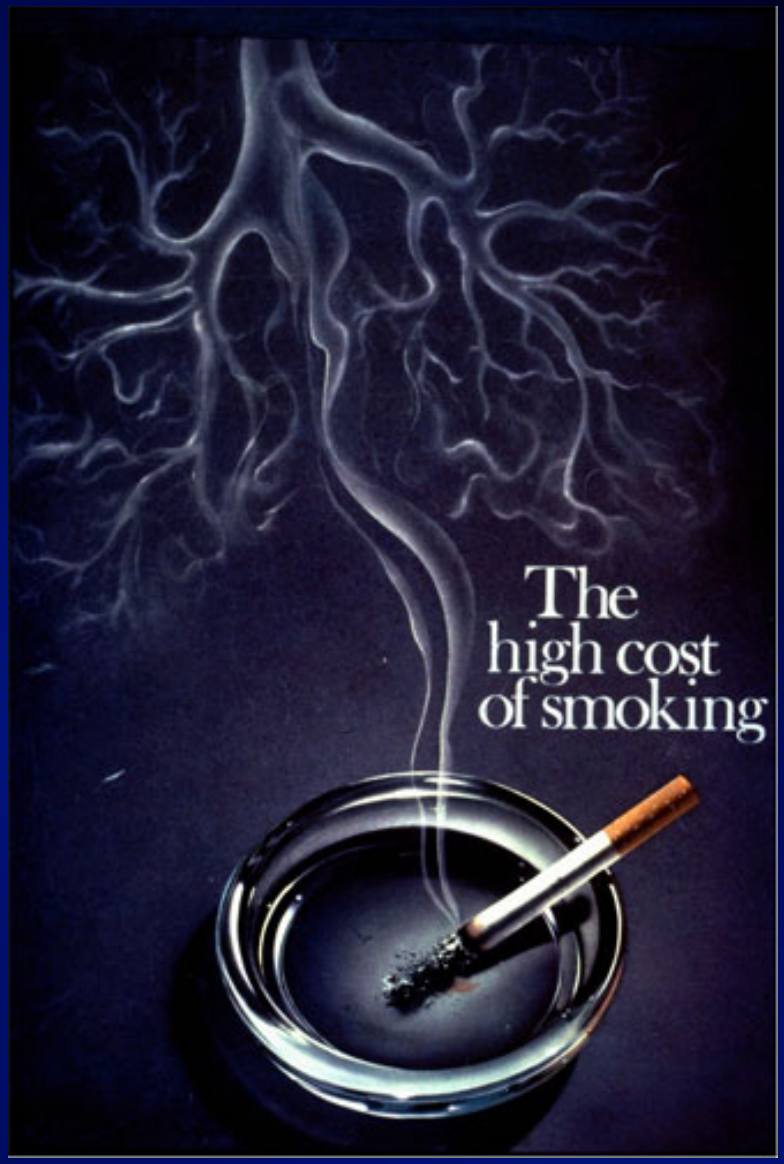
Cockroach

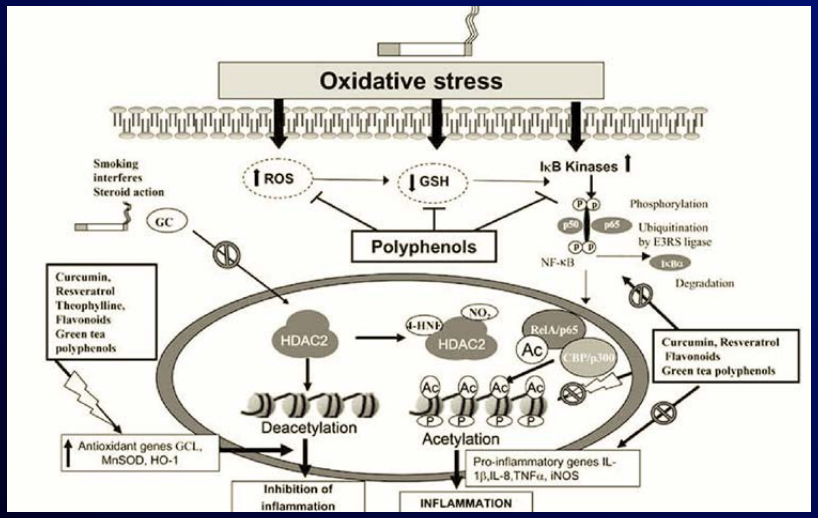
Fungi

Cat

Smoking Cessation/Eliminate ETS

- Over 20% of asthmatics smoke
- Cigarette smoke:
  - Increases mucous production
  - Causes destruction of cilia
  - Induces bronchospasm
- ETS has been shown to be equally detrimental as smoking
- Induces resistance to steroids





Eur Respir J 2009; 33:1010–1017

Risk Factors for Severe Asthma Exacerbation

- Equal among mild, moderate, and severe asthma*
- Key risk factors:
  - Ever been intubated or in ICU for asthma
  - Hospitalized in last year
  - Deficiency in self-management skills
- Predictors of health care utilization:
  - Score of < 20 on Asthma Control Test (ACT)
  - Poor perception of dyspnea

*** Clin & Exper Allergy 2007; 37:552-557**

Factors Influencing the Heterogeneity of Asthma Control: Poor Perception of Dyspnea (POD)

113 Asthmatics Evaluated

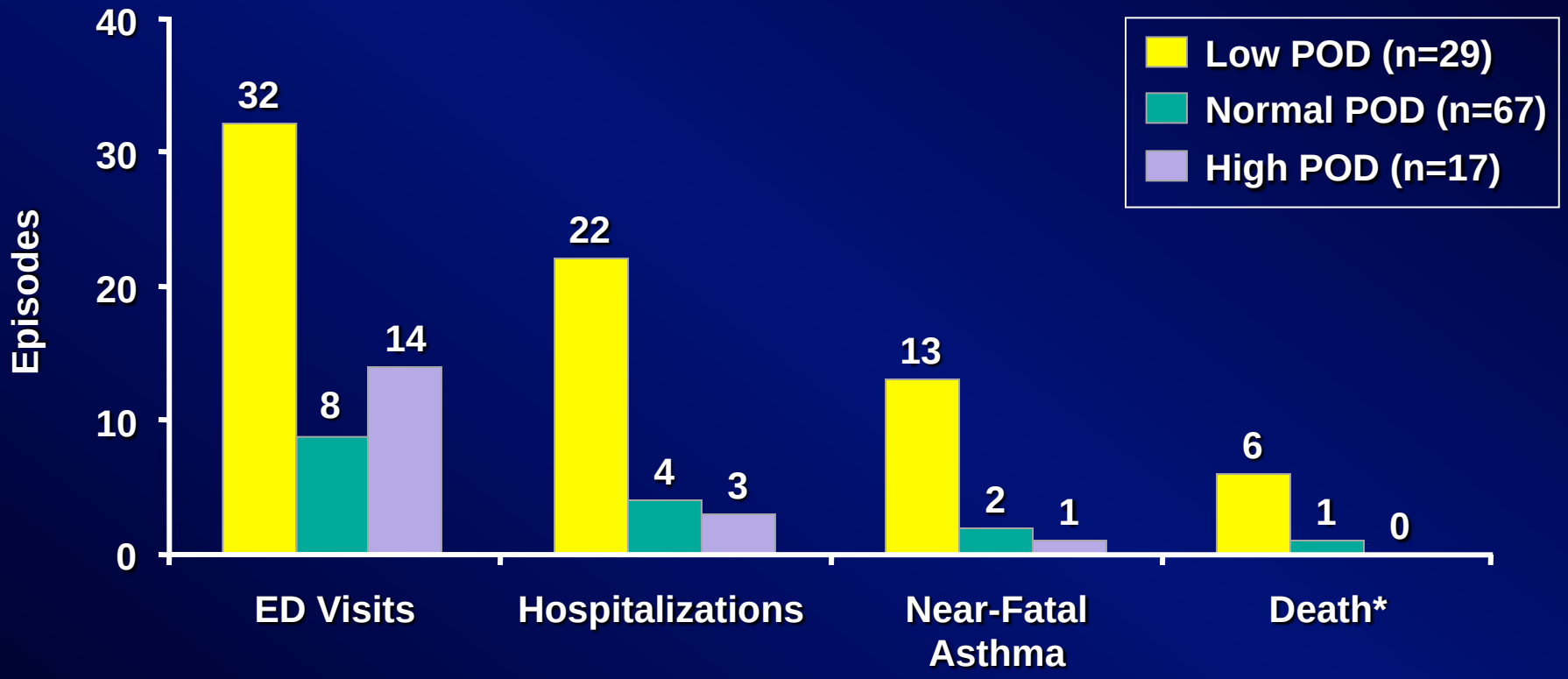
- **Breathe against 2-way valve load of 0-, 5-, 10-, 20-, and 30-cm H_2O for 1 minute**
- **Dyspnea defined as modified Borg scale**
- **POD**
  - **Low 29 (26%)**
  - **Normal 67 (59%)**
  - **High 17 (15%)**

***Puffs/day.**

Magadle R et al. *Chest*. 2002;121:329-333.

- **β_2-Agonist use in 4 weeks***
  - **Low 1.7/day**
  - **Normal 2.4/day**
  - **High 4.1/day**
- **Patients with asthma and a low POD had tendency toward**
  - **Older age**
  - **More females**
  - **Longer duration**
  - **More severe**
- **Documented events over 2 years**

Poor Perception of Dyspnea (POD)



***Of deaths in the low POD group, 4 were asthma related, 2 were unknown.**

Multiple studies now that show underpercievers and life-threatening asthma may have a 20% mortality from asthma

Asthma Control Test™ (ACT)

		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	
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	
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	
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	
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	

Well controlled ≥ 20; 16-19 not well controlled, ≤ 15 very poorly controlled
Available at: http://www.asthmacontrol.com.

Patient Total Score

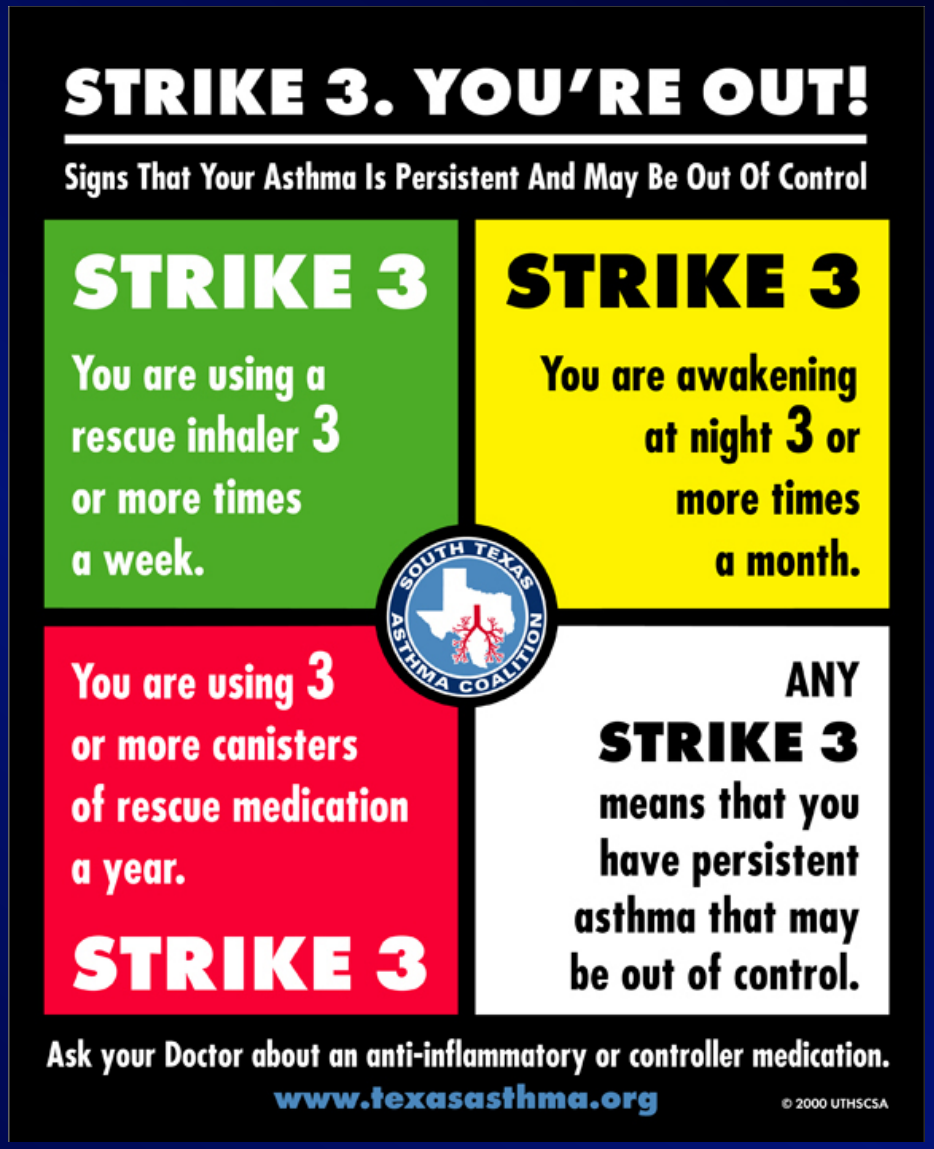
- **ACT < 20 best predictor of asthma control**

ASTHMA 2013

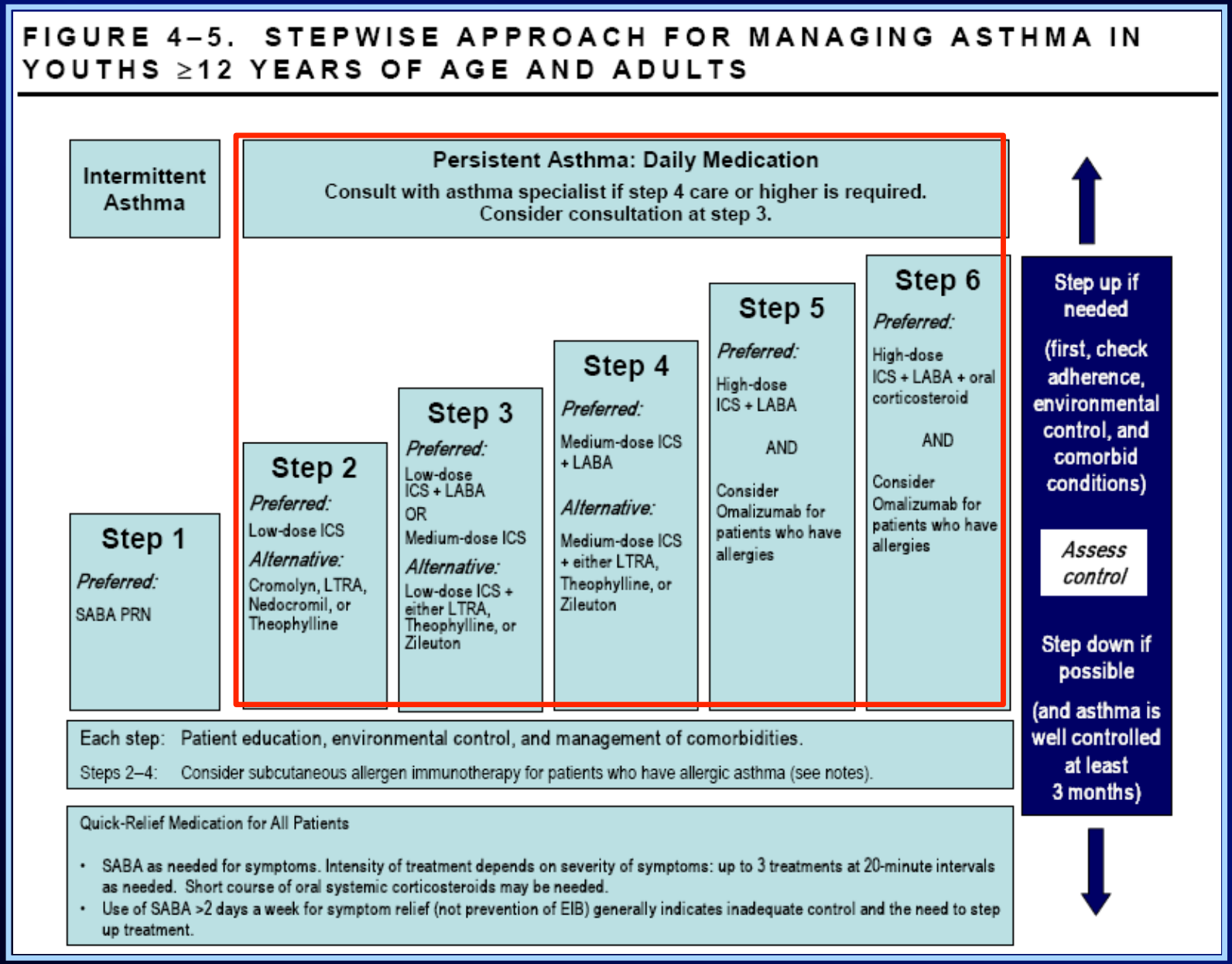
- **Maximizing therapy**
- **Controversies in asthma care**

What is Persistent Asthma?

- Use of rescue inhaler each week
- Nocturnal awakenings/ month
- Number of canisters per year of rescue medications
  - More reliable index
  - Two puffs 3x/week = 3.3 canisters/year

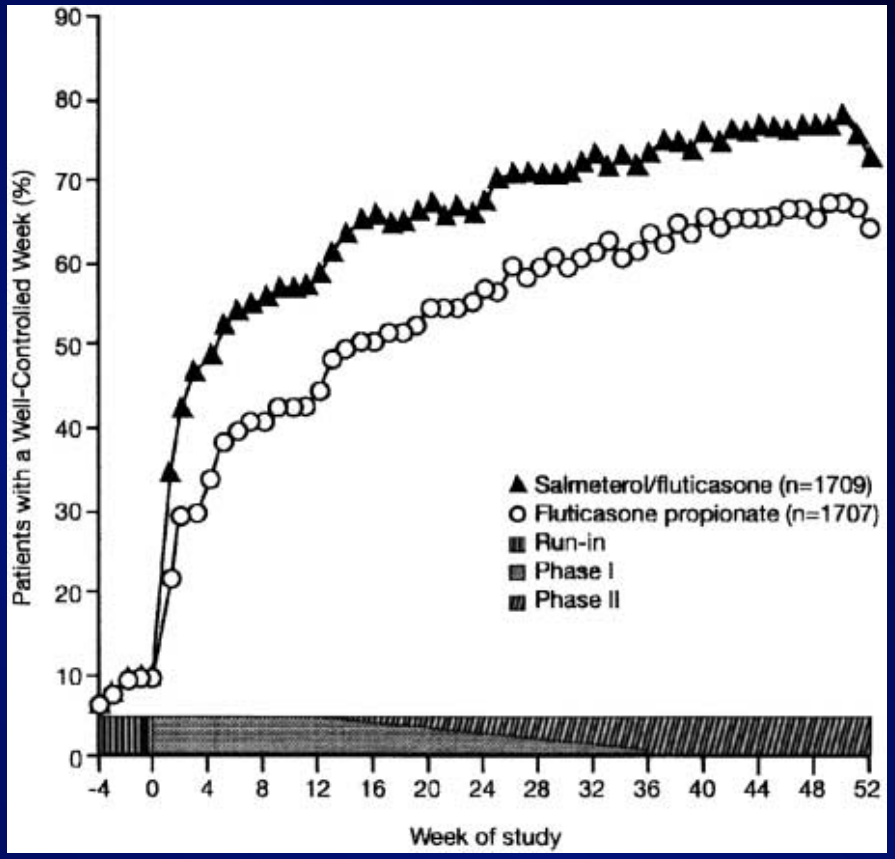


NAEPP Guidelines to the Management of Asthma



Can Guideline-defined Asthma Control Be Achieved?

- **GOAL Study**: Double blind RCT
  - Steroid naive or "low" dose ICS
  - Age 12-80 (n = 3421)
- Total control =31%
- Well controlled = 59-71%
- Prednisone .5 mg/kg x10 days improved control by 5-10%
- Exacerbation rate ≈ 10%
- Conclusion: <u>20%</u> not well controlled on steroids/LABA



Am J Respir Crit Care Med 2004,170 (8): 836–44

Theophylline

Rationale:

- Long-acting bronchodilator by non-selective inhibition of phosphodiesterases
- Anti-inflammatory effects:
  - ↓ Infiltration of lymphocytes and eosinophils into the airway
  - ↓ T-cell proliferative response cytokine production.
  - ↑ Apoptosis of eosinophils

Sullivan P, et al. Lancet 1994; 343: 1006-8.
Ohta K, et al. Clin Exp Allergy 1996;26(Suppl 2):10-5.
Ito K, et al. Proc Natl Acad Sci U S A 2002;99:8921-6.

Theophylline

- **Spears M, et al. Eur Resp J. 2009 (n = 68)**
  - ICS vs. theophylline + ICS vs. theophylline alone. In asthmatic *smokers*.
  - The combination of theophylline + ICS provided the best results improving ACQ scores and pulmonary function.
- **Nie H , et al. Resp Med. 2013** (n = 325)
  - ICS/LABA + theophylline vs. ICS/LABA + placebo in a randomized, parallel-group study (24 weeks)
  - Patients receiving theophylline had fewer exacerbations (≥ 1) 30 vs. 47 % (p = 0.004).
  - Theophylline group had significant decreased in sputum eosinophils and eosinophilic cationic protein.

Theophylline

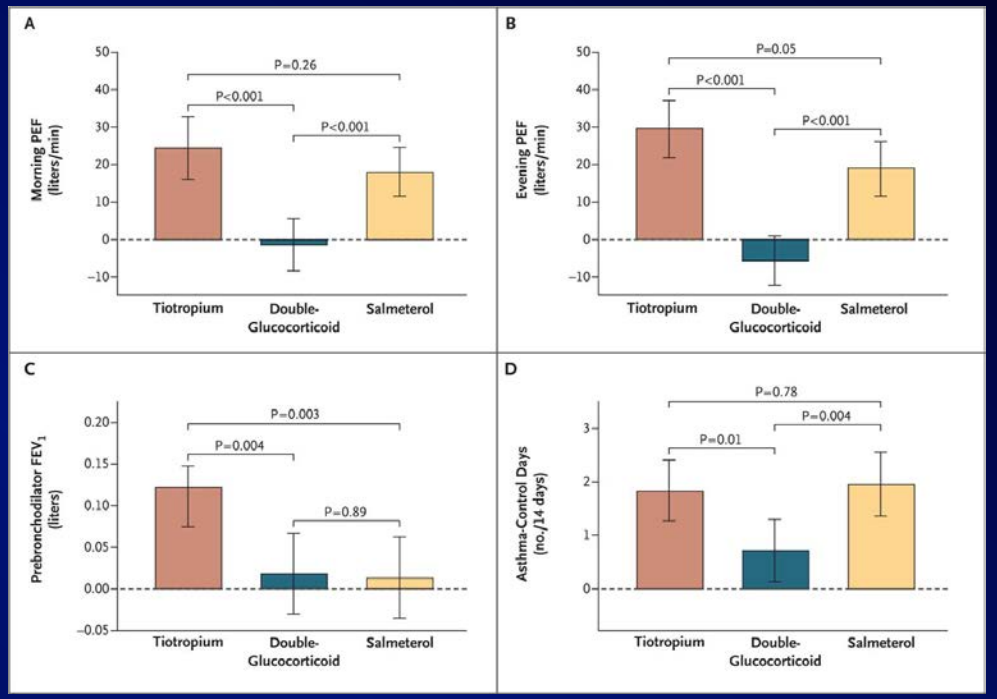
- **Pros:**
  - Modest bronchodilation
  - Possible anti inflammatory effects
  - Possible reversal of steroid resistance
  - Convenient dosing
  - **Potentially more beneficial in asthmatic smokers**
- **Cons:**
  - Need to monitor levels
  - Potentially severe side effects
  - Interaction with other medications
  - Limited evidence of effectiveness

Long acting muscarinic antagonists

- ✓ **Rationale:**
  - Activation of the parasympathetic (acetylcholine) system causes bronchoconstriction, bronchial vasodilation and mucus secretion. **Asthma may cause increased parasympathetic afferent stimulation.**
- ✓ **Approved for COPD:**
  - **Tiotropium**: reduces smooth muscle contraction and mucus secretion.
  - **Aclidinium**: newly approved. Few data on asthma.

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

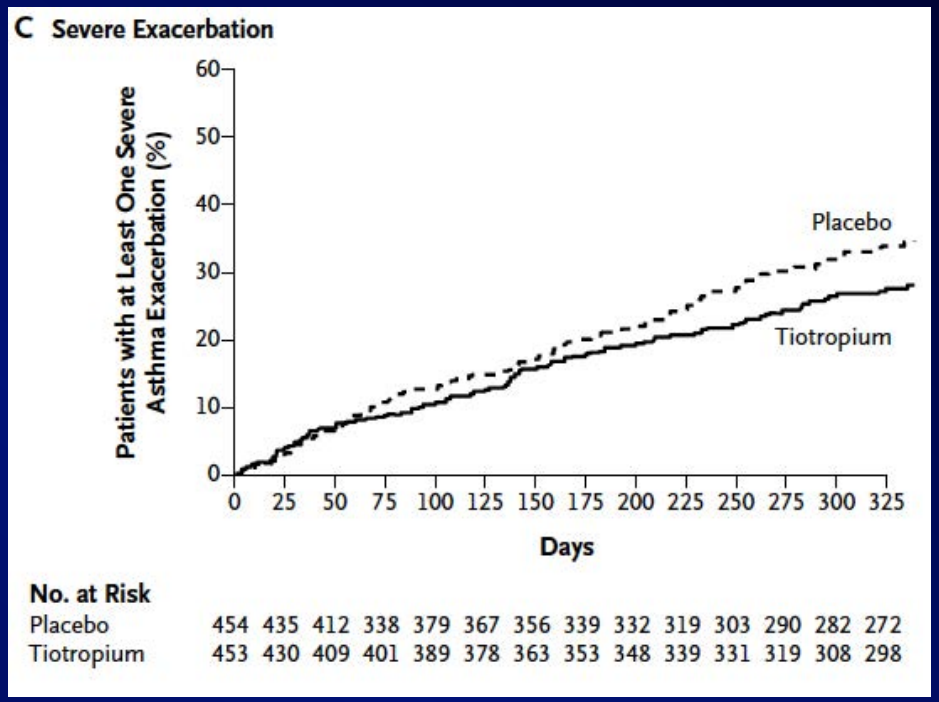
- TALC study
  - Poorly controlled on ICS
    - Double ICS
    - LABA (salmeterol)
    - LAMA (Tio)
- Primary endpoints
  - PEFR
  - FEV_1
  - Asthma control days
- LAMA = LABA > ↑ ICS
- No long term data; select subset of subjects



N Engl J Med 2010;363:1715-26
October 28,2010

Long acting muscarinic antagonists

- Kerstjens et al. J Allergy Clin Immunol. 2011 **(n = 107)**
  - Tiotropium as an add-on to ICS + LABA.
  - Poorly controlled, severe asthma: tiotropium improved FEV_1 over 24 hrs
- Kerstjens et al. ***(n = 912)***
  - Increased time to first exacerbation by 56 days
  - 21% reduction in the risk of a severe exacerbation*



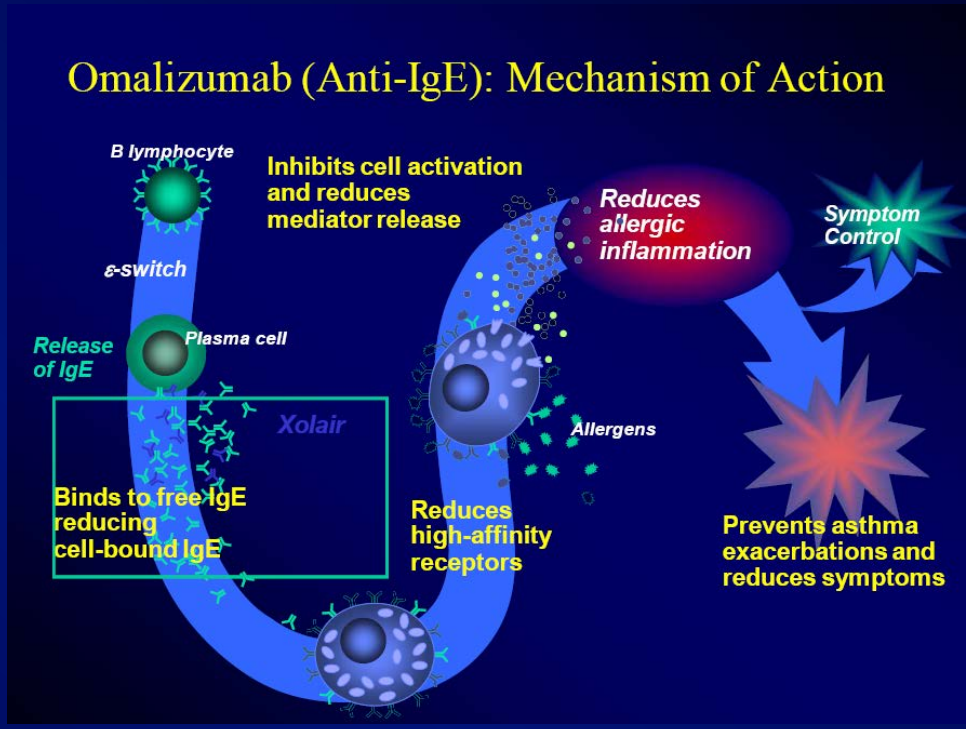
NEJM 2012;1198-1207

Is this clinically meaningful?

* Note: "Severe" = Double ICS x 3 days
FEV1 increased 88 +/- 31 ml

Omalizumab: Indications

- Patients with allergic asthma ages 12 years & older (6 years old: Europe)
- Step 5-6 NAEPP Guidelines -2007
- IgE level: 30-700 IU/ml
- One positive perennial antigen by skin test or RAST/Immunocap



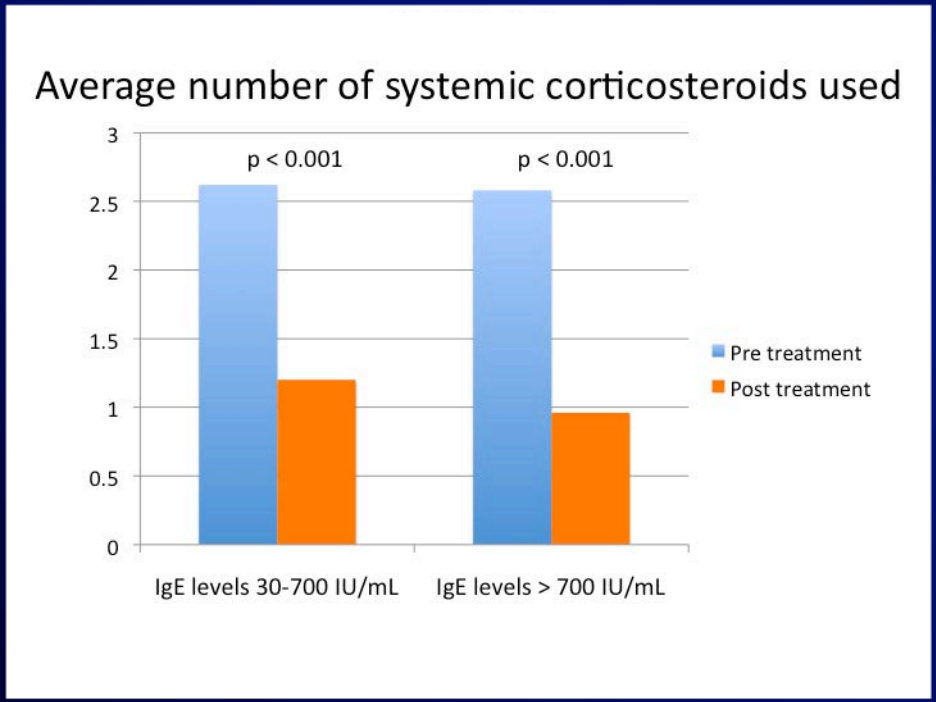
Omalizumab

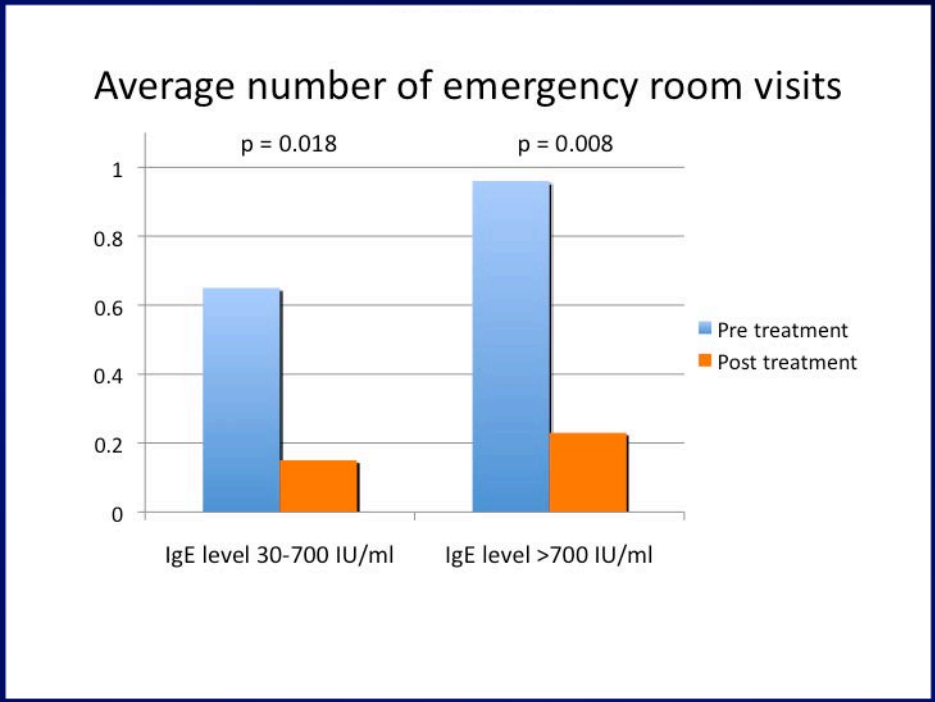
- Evidence:
  - Multiple studies have shown efficacy in:
    - ✓ ↑ Quality of life
    - ✓ ↓ Exacerbations
    - ✓ ↓ ER visits
    - ✓ ↓ Hospitalizations
    - ✓ ↓ Steroid requirements

Busse W, et al. J Allergy Clin Immunol. 2001 Aug;108(2):184-90.
Solèr M, et al. Eur Respir J. 2001 Aug;18(2):254-61.
Holgate S, et al.. J Allergy Clin Immunol. 2005 Mar;115(3):459-65.
Humbert M, et al. Allergy. 2005 Mar;60(3):309-16.
Hanania NA, et al. Ann Intern Med. 2011 May 3;154(9):573-82.

Omalizumab

Omalizumab in patients with IgE levels of 30-700 vs. above 700 IU/ml (n = 52)





Maselli D, Peters J, et al. Ann Allergy Asthma Immunol. 2013 Jun;110(6):457-61.

Omalizumab

- **Pros:**
  - **Clear evidence of ↓ of exacerbations, ER visits, hospitalization & oral steroid requirements**
- **Cons:**
  - **High cost**
  - **Frequent visits required (every 2-4 weeks)**
  - **Subcutaneous dosing**
  - **Not clear when to stop therapy**
  - **Possibly limited therapeutic window**

ASTHMA 2013

- **Maximizing therapy**
- **Controversies in asthma care**

Measurement of Nitric Oxide? ATS Guidelines

- < 25 ppb (20 ppb in children) - eosinophilic inflammation and responsiveness to corticosteroids are less likely
- >50 ppb (> 35 ppb in children) eosinophilic inflammation and responsiveness to corticosteroids in sx patients is more likely
- 25-50 ppb (20–35 ppb in children) depends on the clinical context

Reasons to Measure Nitric Oxide

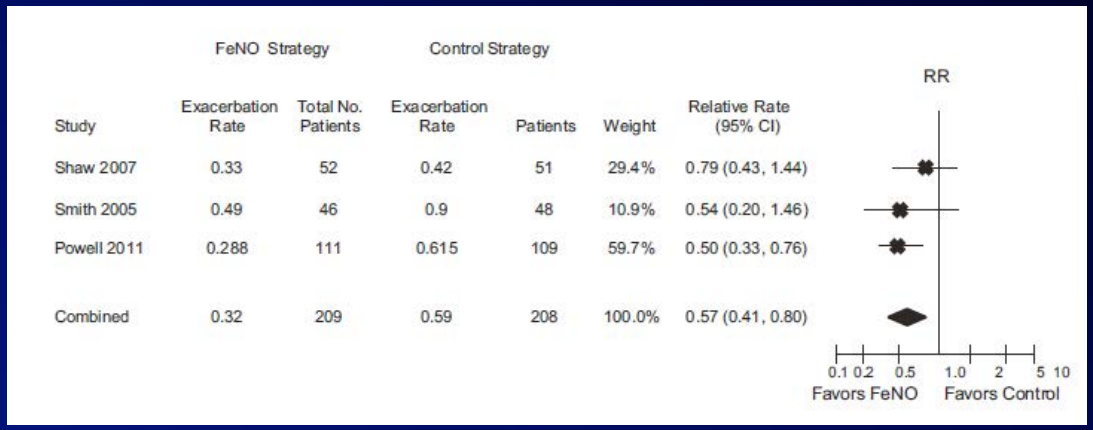
- Identify the eosinophilic asthma phenotype
- Assess potential response or failure to ICS
- Assist in the evaluation of adherence to anti-inflammatory medications
- Guide changes in doses of anti-inflammatory medications

❖ Studies have not been able to show FENO impacts lung function, QOL, or rate of asthma exacerbations but increased ICS use

Szefler SJ et. al. Lancet 2008;372:1065-72

Use of FENO in Management of Asthma: Pro

- **Initial studies:**
  - **Often mild asthma**
  - **Small numbers**
  - **Evaluated number of pts with exacerbations**
- **Donahue analysis**
  - **Evaluated total number of exacerbations**



Reanalysis of Cochrane Studies

Step wise protocol for ICS management based on FENO

	Men	Women	ICS adjustment
FeNO	<19	<21	Decrease dose 1 step
	19-23	21-25	No change in ICS dose
	24-30	26-32	Increase dose 1 step
	>30	>32	Increase 2 steps

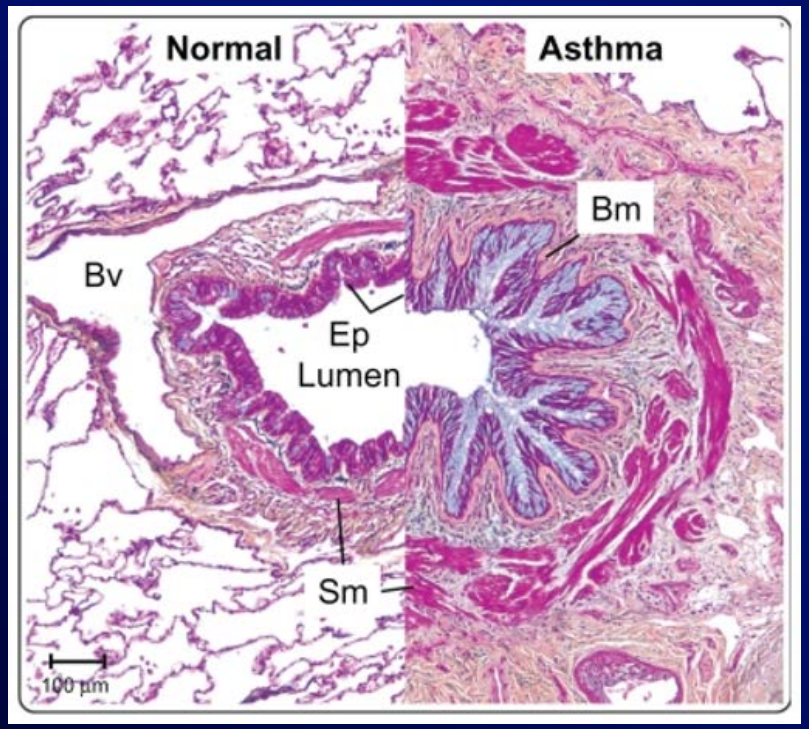
Ongoing study: using FENO to titrate ICS

Respir Med 2013;10(7):943-52

Bronchial thermoplasty (BT)

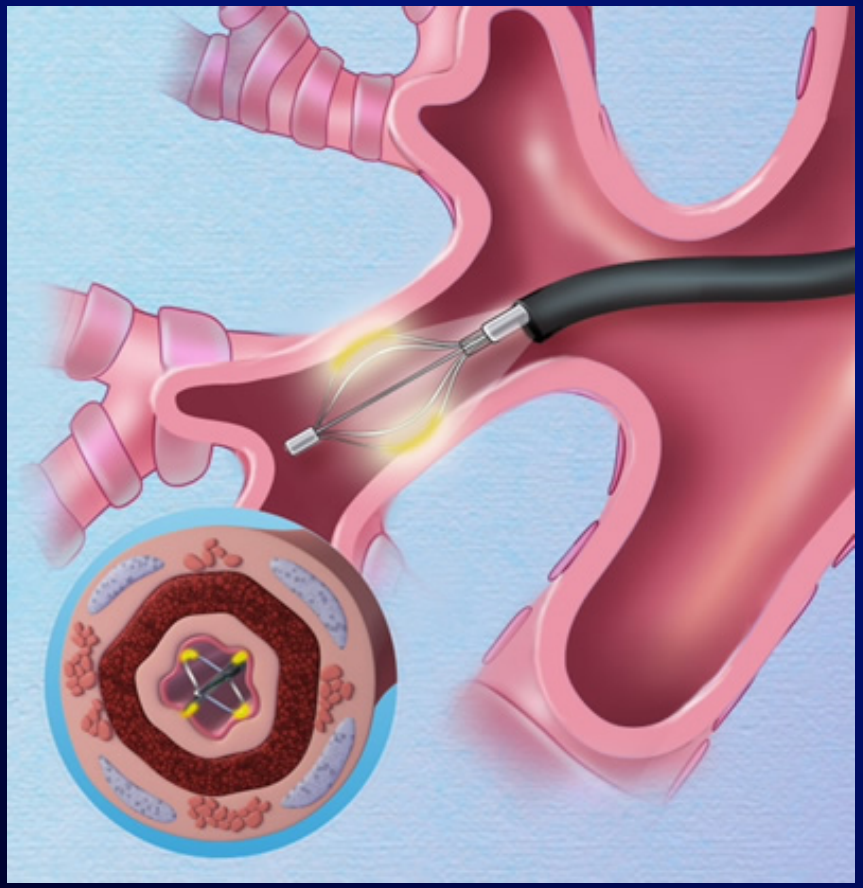
Rational or Irrational ?

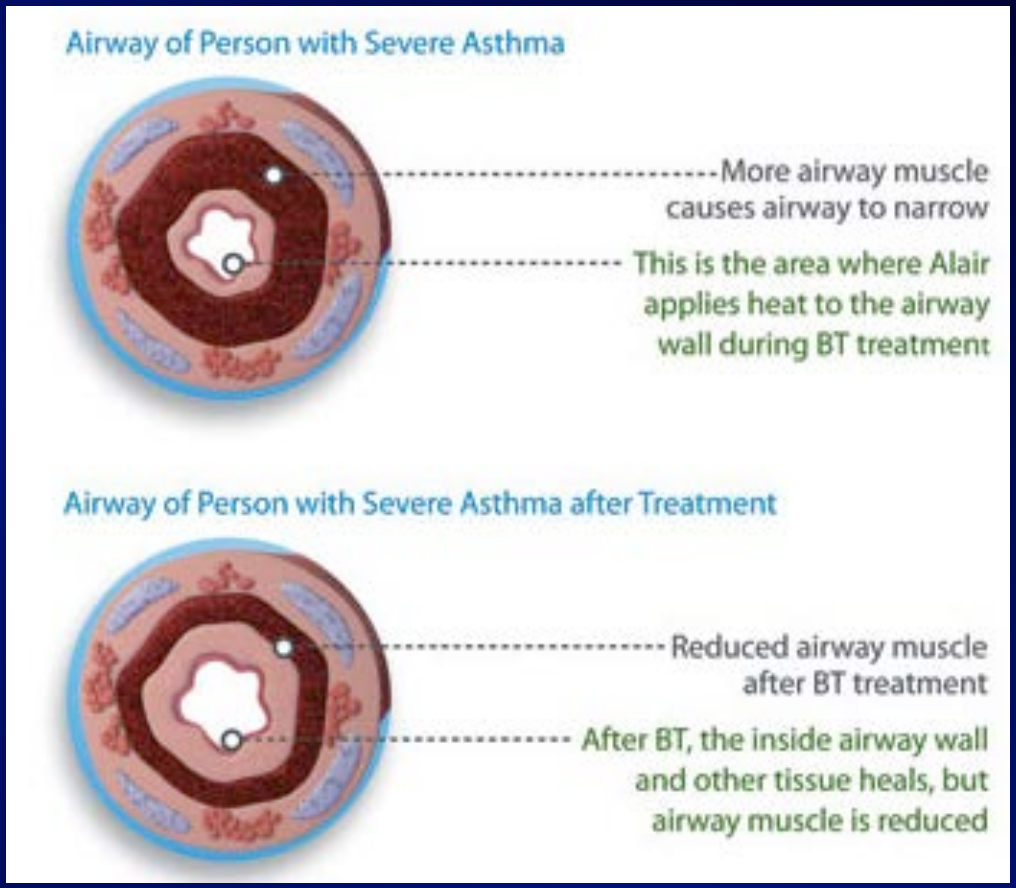
- Asthma: characterized by airway remodeling with s airway smooth muscle (ASM) hyperplasia/hypertrophy
- BT: can decrease significantly the ASM mass (via radiofrequency energy/ablation)



Airway remodeling

Bronchial thermoplasty





Bronchial thermoplasty

- **Pros:**
  - **Some evidence of reduction of symptoms**
  - **Apparent lasting effects (≥ 5 years)**
- **Cons:**
  - **High cost**
  - **Early exacerbation rate despite pre-treatment with oral steroids**
  - **Need for 3 bronchoscopies**

Can Asthma Be Prevented ?

- Concept: Maternal and epigenetic factors (how environment changes gene activity) are key factors in the development of allergy and asthma
- Current recommendations:
  - Breast feed and avoid cow's milk first 4-6 months
  - Use hydrolyzed formula if breast feeding not possible
  - Avoid ETS during pregnancy and lactation
- Controversial data:
  - Change infants microbiome (probiotics)
  - Early introduction of peanuts & hen's eggs
  - Early antigen avoidance (Isle of Wright Study)


Questions?