Asthma and Bronchial Thermoplasty

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Disclosures

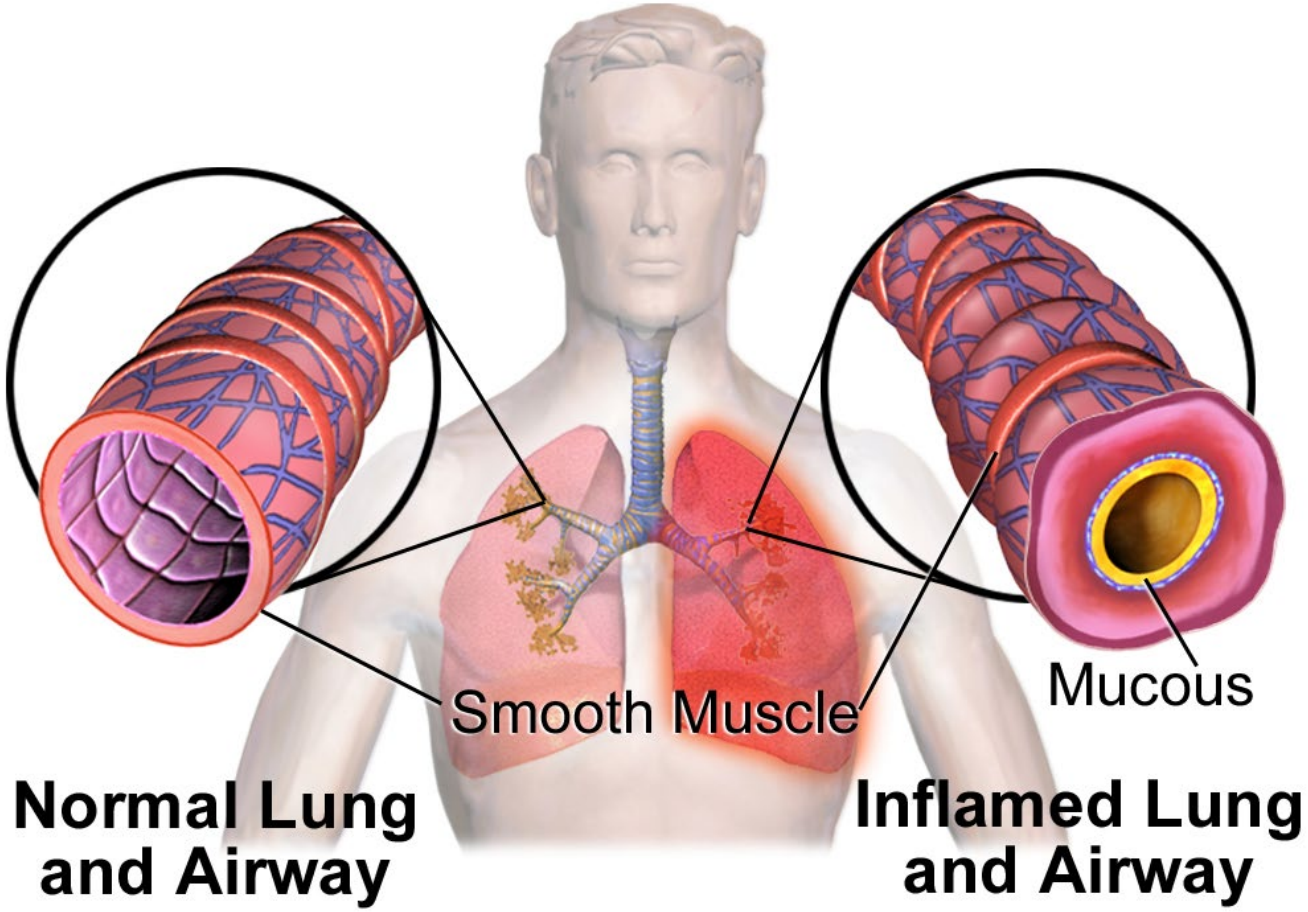
- I have no financial disclosures.

Objectives

- Definitions
- Basic Science and pathophysiology
- Epidemiology
- Classification
- Therapy—The old and the New
- Bronchial Thermoplasty (BT)
- The Data on BT
- Our Data
- Clinical Case report

Asthma Defined

- **Disease of Chronic inflammation:**
- -Inflammatory cells/infiltrates: Eosinophils, Lymphocytes, neutrophils
- -Mast cell activation, epithelial cell injury
- -Abnl smooth muscle function and neovascularization
- **Inflammation contributes to:**
- -Respiratory Symptoms and exacerbations
- -Airflow limitation/partial airway obstruction
- -Airway hyperresponsiveness
- -Disease chronicity with chronic remodeling



Jeffery PK, Am J Respir Crit Care Med, 2001: 164:S28

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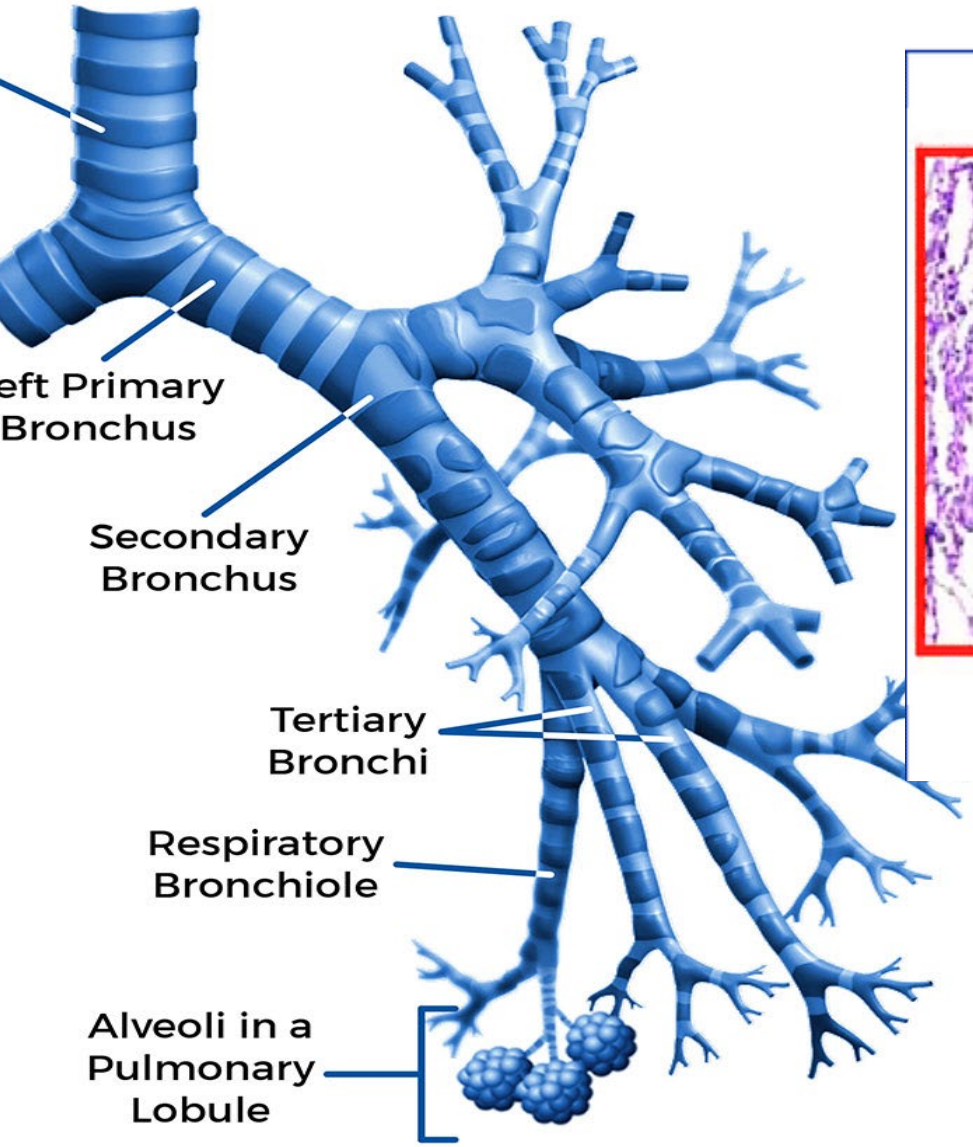
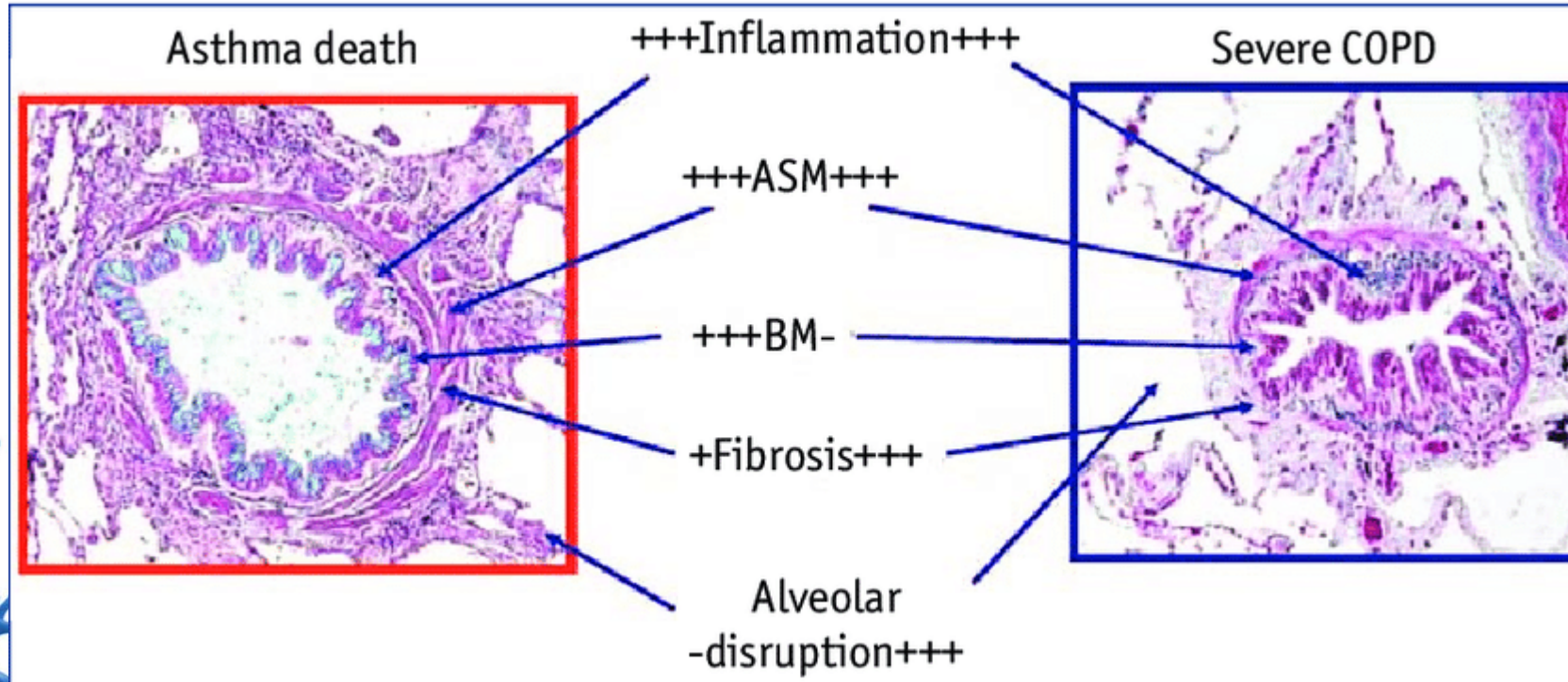
Asthma vs. COPD





Asthma is both:
Large and
Small airway inflammatory disease

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Asthma Pathophysiology

INFLAMMATION

- Genetic predisposition
- Innate vulnerability
- Atopy/allergy
- Environmental triggers
- Inflammation underlies the disease process
- Phenotype varies by patient
- Clinical symptoms vary by patient over time

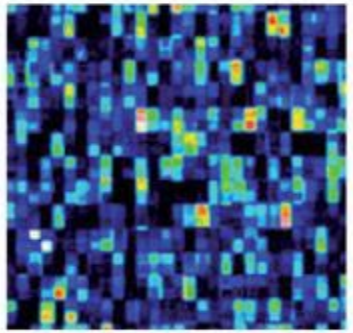
IMPACT

- Airway obstruction
- Airway Hyperresponsiveness and Bronchospasm
- Airway remodeling

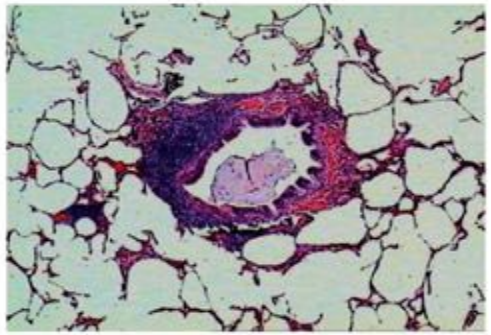
NIH Hear t and Lung and Blood Insitute insitute. National Asthma Education and Prevention Program. Expert Panel Report 3. guidelines for the Diagnosis of Asthma--Full Report 2007

Asthma is Heterogeneous and Complex

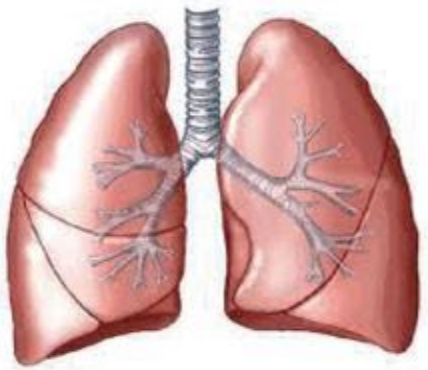
Genes



Gene expression



Airway histology



Lung Function

The patient

Severe asthma phenotyping			
Genetics Epigenetics Transcriptome Proteome Metabolome	Microbiome Immunity Inflammation	Remodeling Bronchial hyperresponsiveness Obstruction	Symptoms Comorbidity Quality of life

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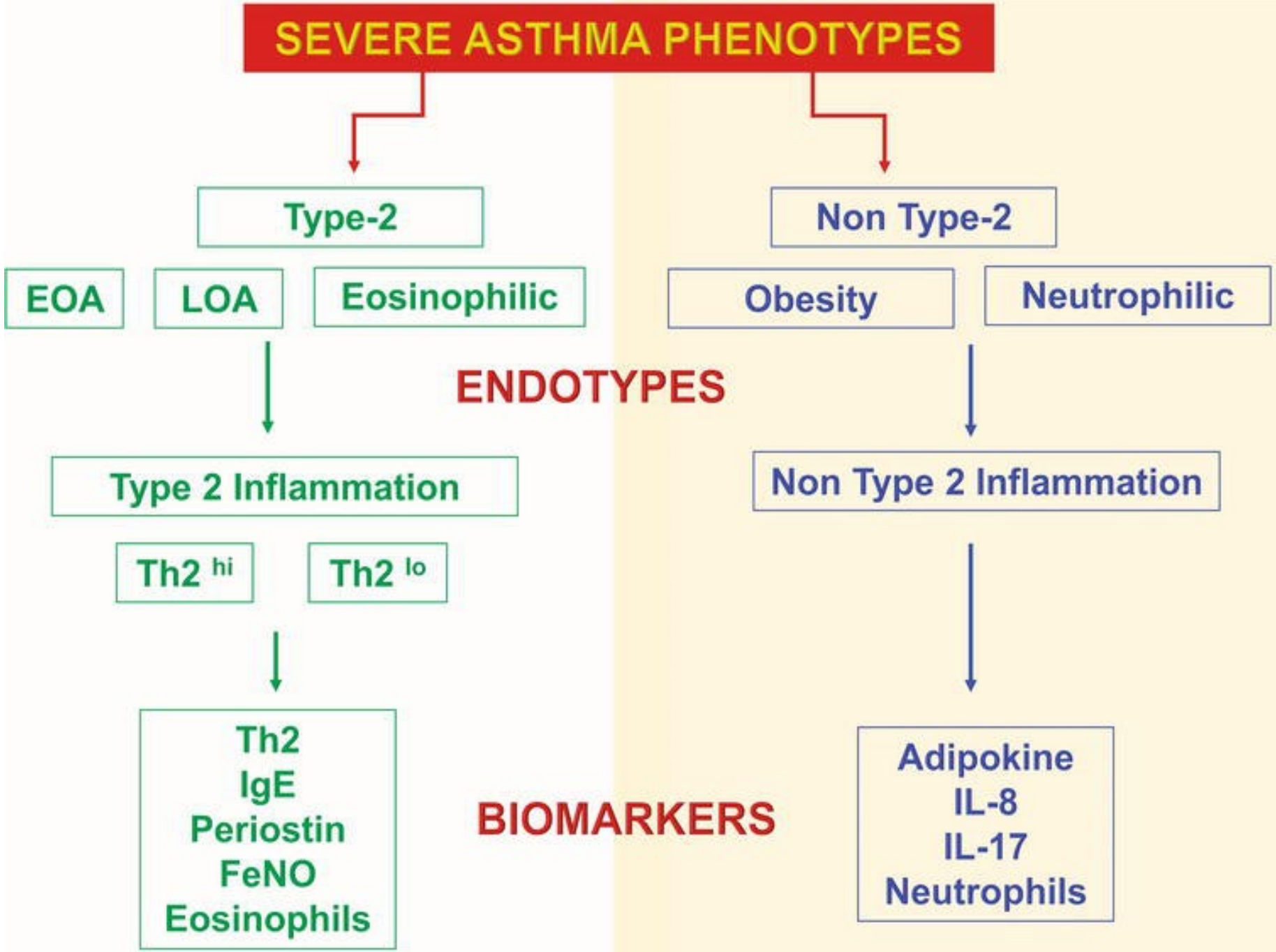

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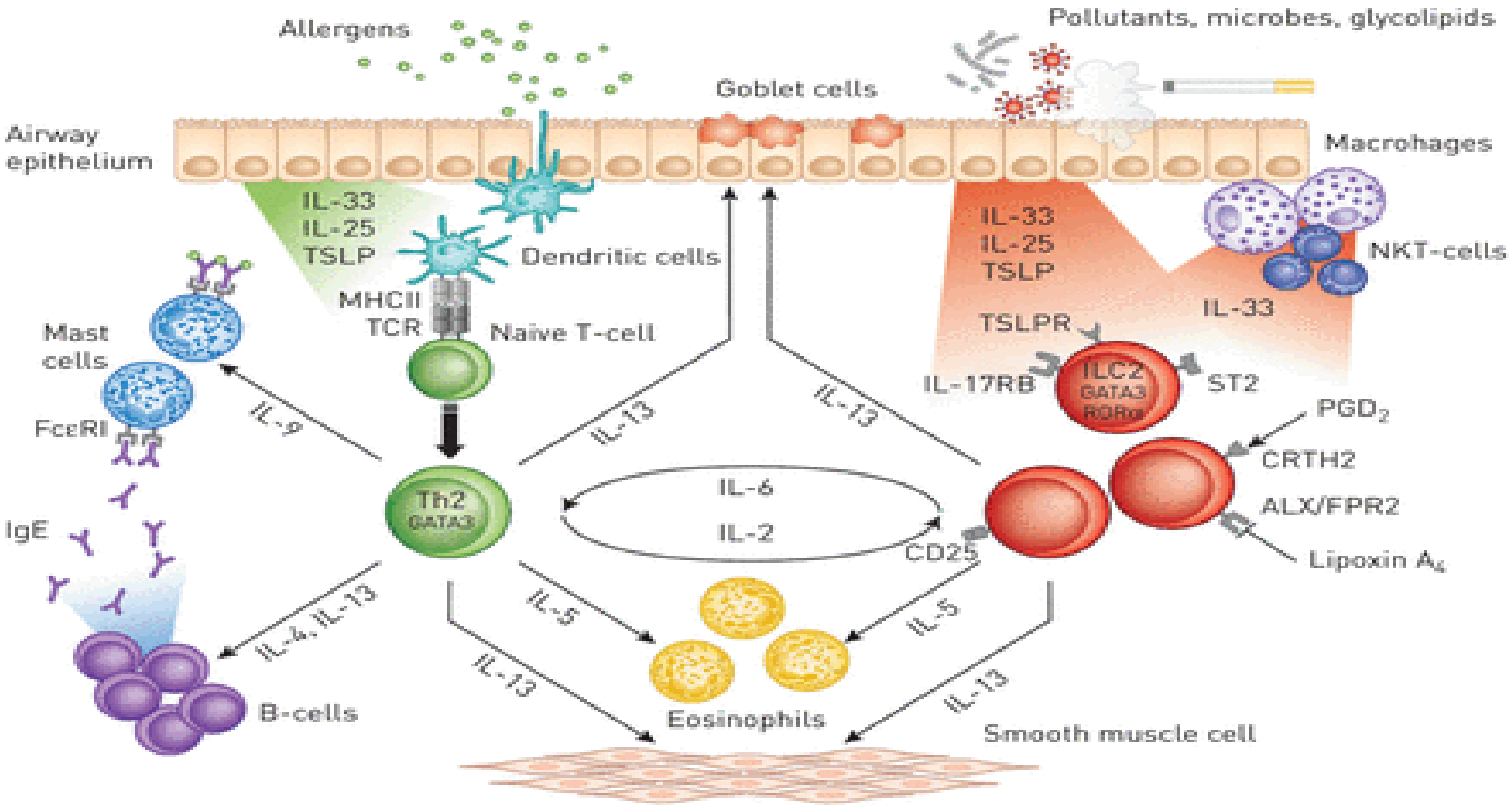

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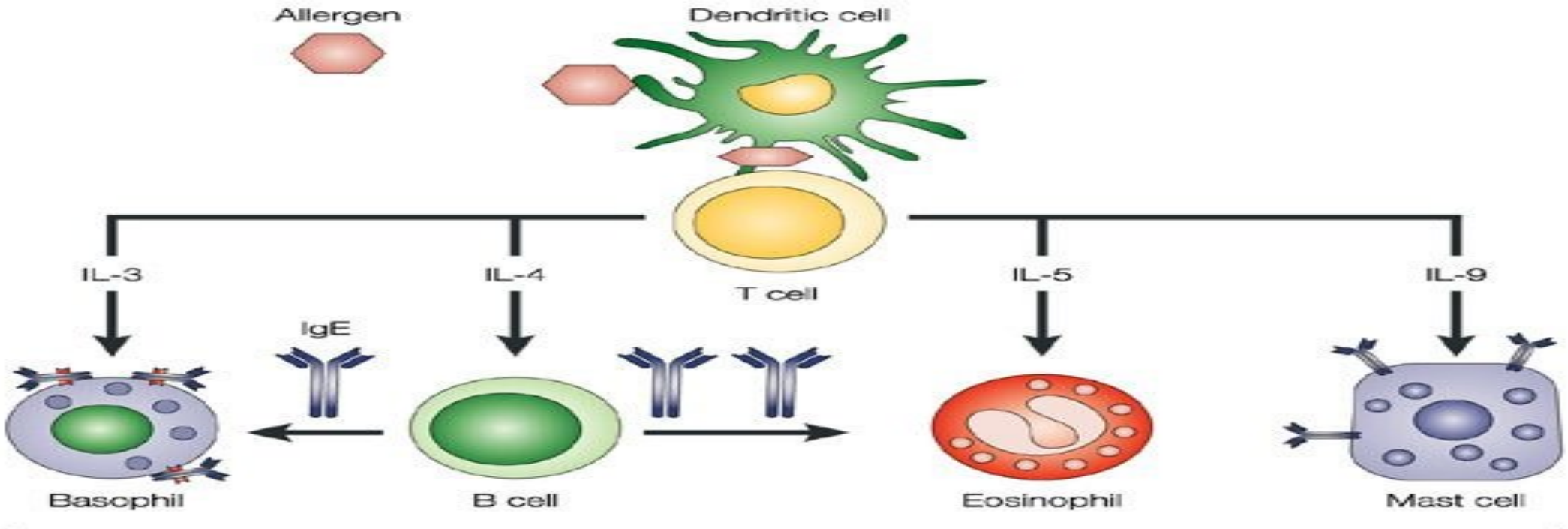

Inflammatory mediators	**Mediators**	**Cytokines**	**Chemokines**
	Histamine	TNF	Eotaxin
	Leukotrienes	IL-4	RANTES
	Neuropeptides	IL-5	TARC
	Prostaglandins	IL-9	MCP-1
	Tryptase	IL-13	MIP-1α
Targets	Nerves	Mucous glands	Blood vessels
Symptoms	Sneezing, itching	Rhinorrhea	Congestion

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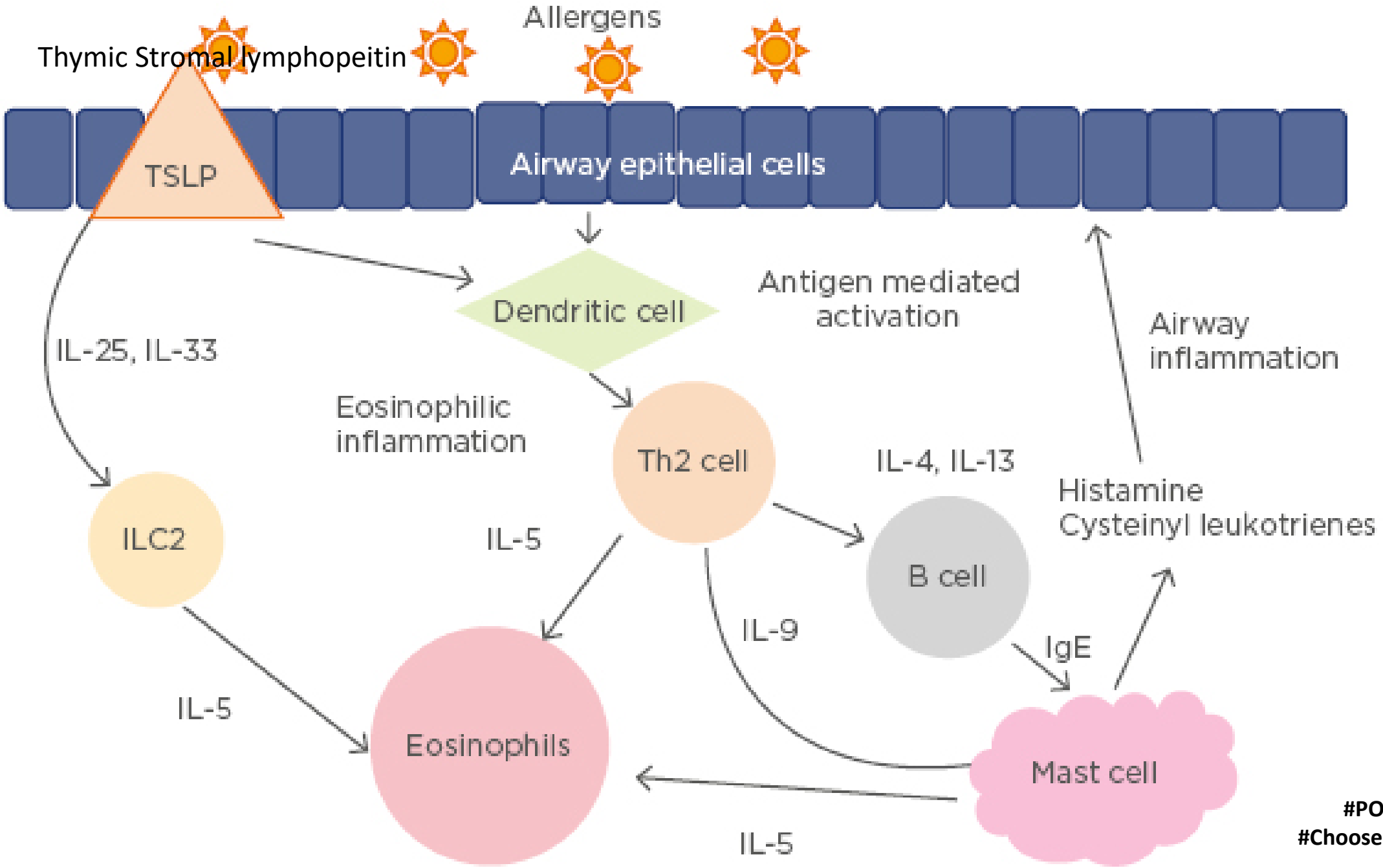

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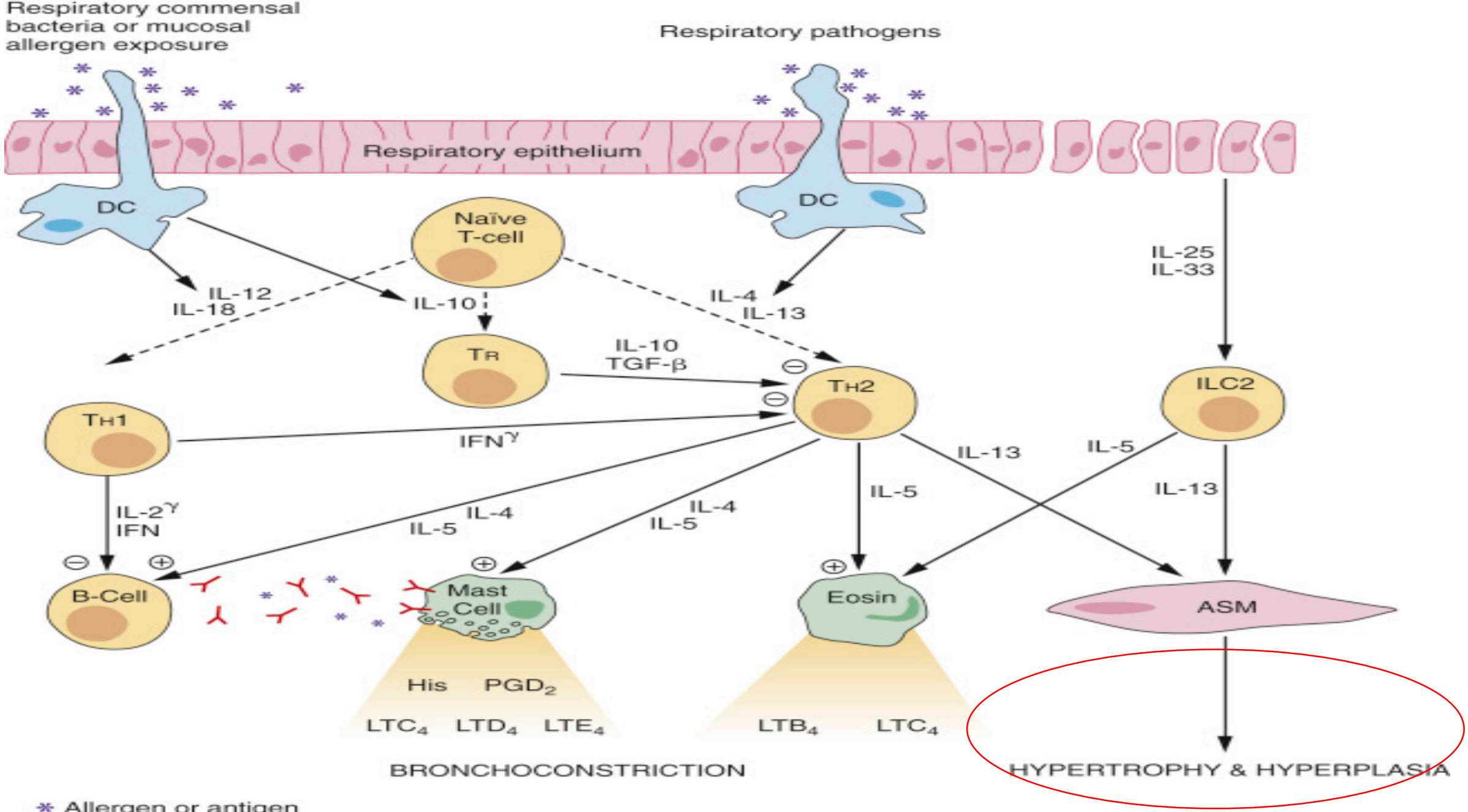

DC=Dendtritic cell

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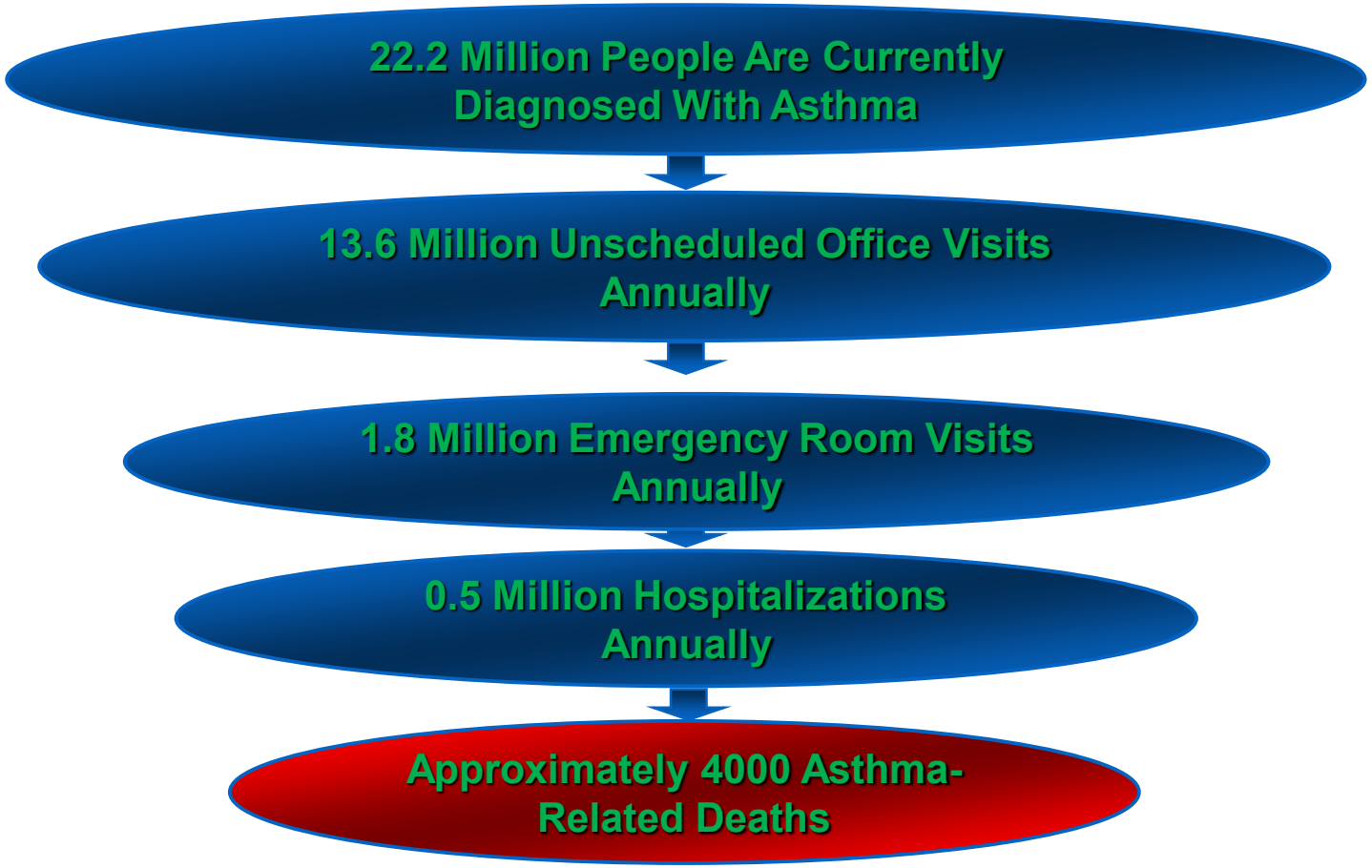
Asthma

Prevalence, Morbidity and Mortality-
HAS NOT CHANGED OVER THE LAST DECADE



Approximately 11 People Die From Asthma Each Day in the US

National Center for Health Statistics, CDC, 2005;
http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.html

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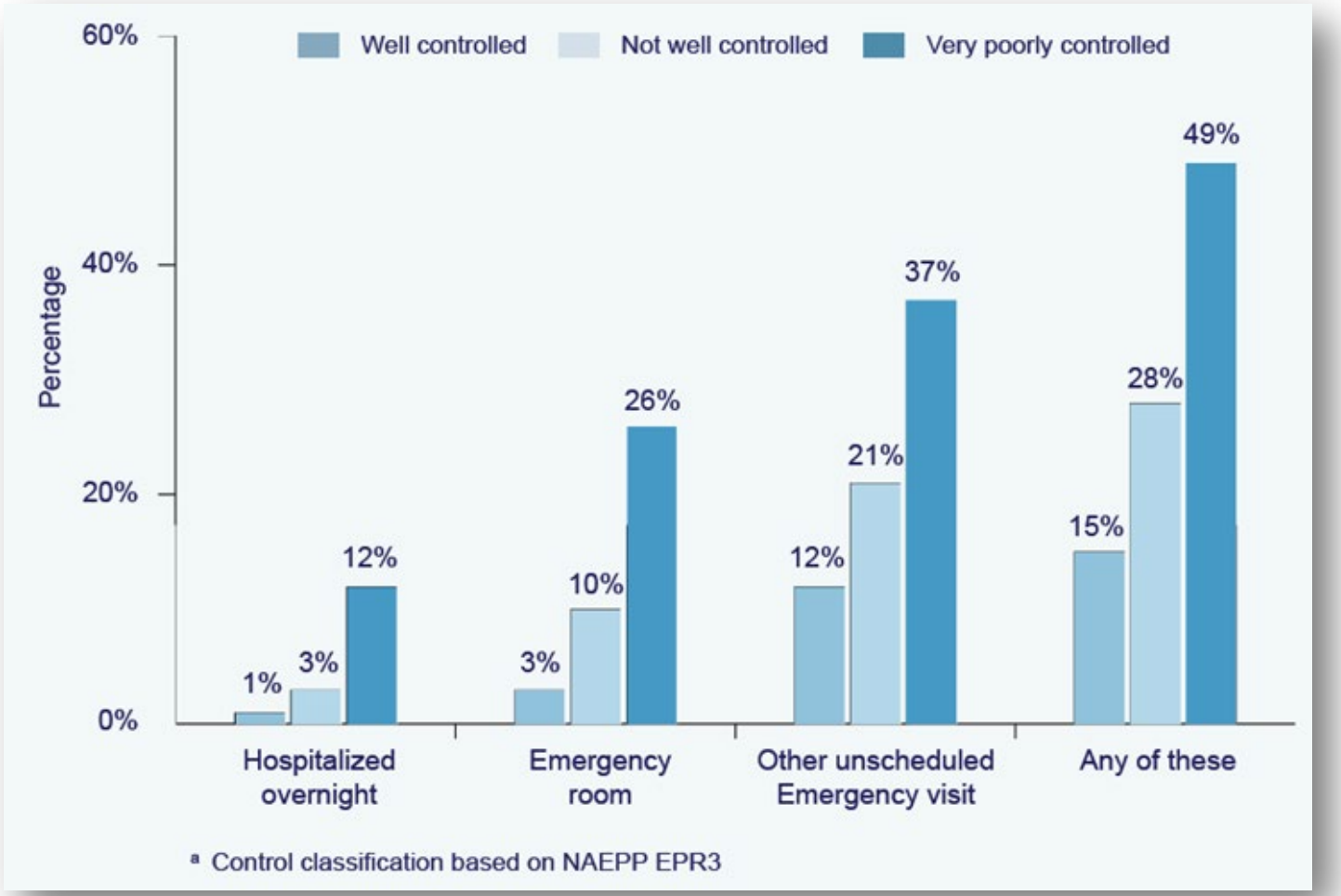
Higher Healthcare Utilization in Poorly Controlled Asthma



Source: Asthma Insight and Management (AIM): A National Survey of Asthma Patients, Public, and Healthcare Practitioners. Executive summary 2009.

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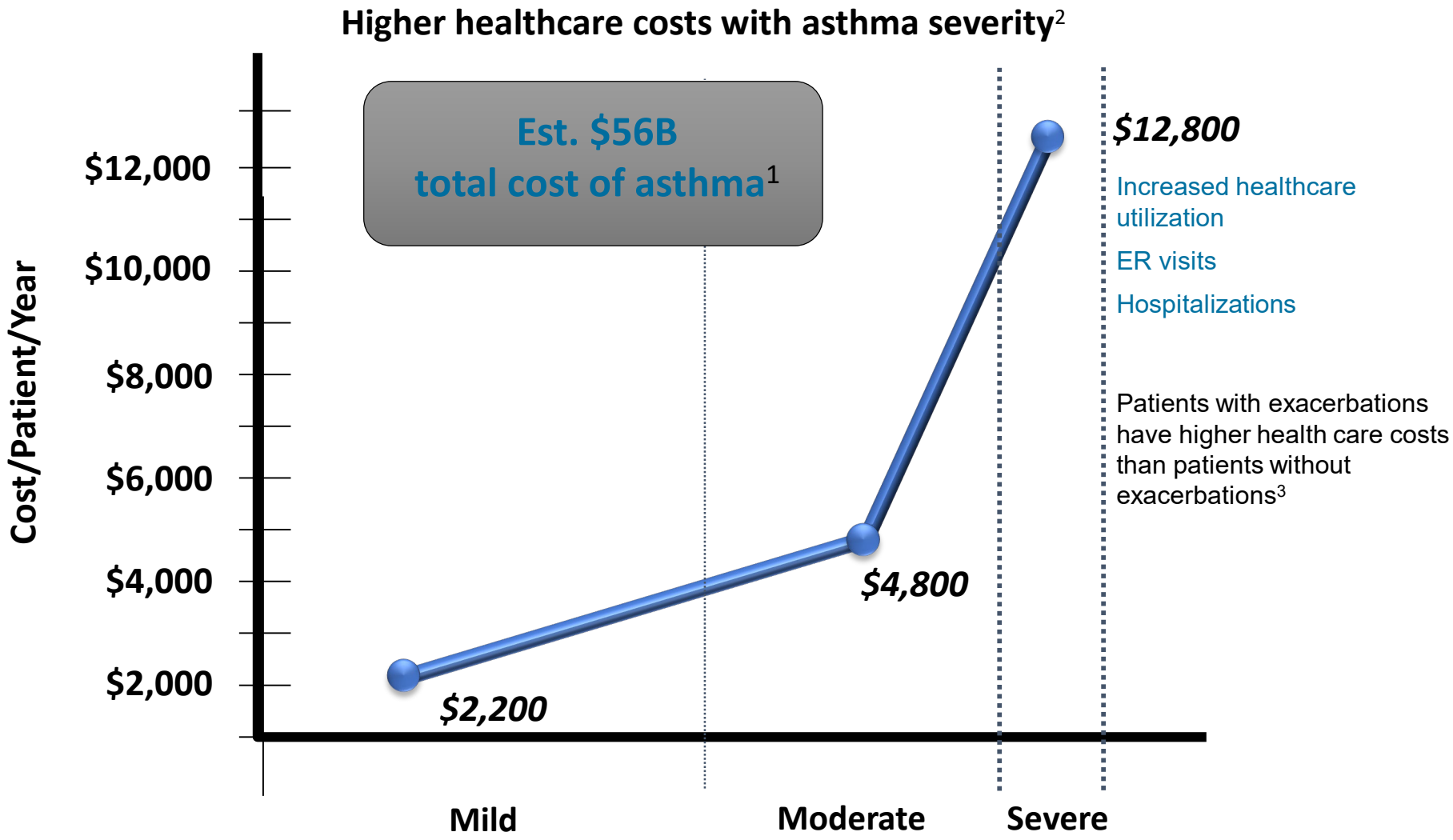
Higher Cost of Severe Asthma



1. Barnett SBL, et al. Costs of asthma in the United States: 2002–2007. J Allergy Clin Immunol 2011;127:145–52.
2. Cisternas M, et al., A comprehensive study of the direct and indirect costs of an adult with asthma. J Allergy Clin Immunol 2003;111(6):1212-1218.
3. American Lung Association, Trends in Asthma Morbidity and Mortality, February 2010 report.

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BOX 1

The definition of severe asthma (according to ERS/ATS 2014) (7)

During treatment with:

- High-dose ICS + at least one additional controller (LABA, montelukast, or theophylline) or
- Oral corticosteroids >6 months/year

...at least one of the following occurs or would occur if treatment would be reduced:

- ACT <20 or ACQ >1.5
- At least 2 exacerbations in the last 12 months
- At least 1 exacerbation treated in hospital or requiring mechanical ventilation in the last 12 months
- FEV_1 <80% (if FEV_1/FVC below the lower limit of normal)

The lower limit of normal (LLN) for FEV_1/FVC can be calculated using appropriate spirometer software (www.lungfunction.org). Current recommendations advocate a FEV_1/FVC <LLN to detect airway obstruction (40). However, if LLN is unknown, in our opinion the formerly universal limit (FEV1/FVC <70% for adults, FEV1/FVC <75% for children) can still be used.

ICS: Inhaled corticosteroid; ACT, Asthma Control Test; ACQ: Asthma Control Questionnaire; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; ERS: European Respiratory Society; ATS: American Thoracic Society; LABA: Long-acting ß2 agonist

Component of Severity		Classification of Asthma Severity (≥12 yrs)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakening	≤2 d/mo	3-4x/mo	>1x/wk but not nightly	Often 7x/wk
	SABA use	≤2 d/wk	>2 d/wk but not daily & not >1x on any day	Daily	Several times per day
	Interference with activity	NONE	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1: >80% predicted • FEV_1/FVC: normal	• FEV_1: >80% predicted • FEV_1/FVC: normal	• FEV_1: >60% but <80% predicted • FEV_1/FVC: reduced 5%	• FEV_1: <60% predicted • FEV_1/FVC: reduced >5%
RISK	Exacerbations requiring oral steroids	0-1/yr	≥2/yr		
		Consider severity and interval since last exacerbation as they may fluctuate over time in any severity category			
Recommended Treatment Step		Step 1	Step 2	Step 3	Step 4 or 5
				And consider short OCS burst	

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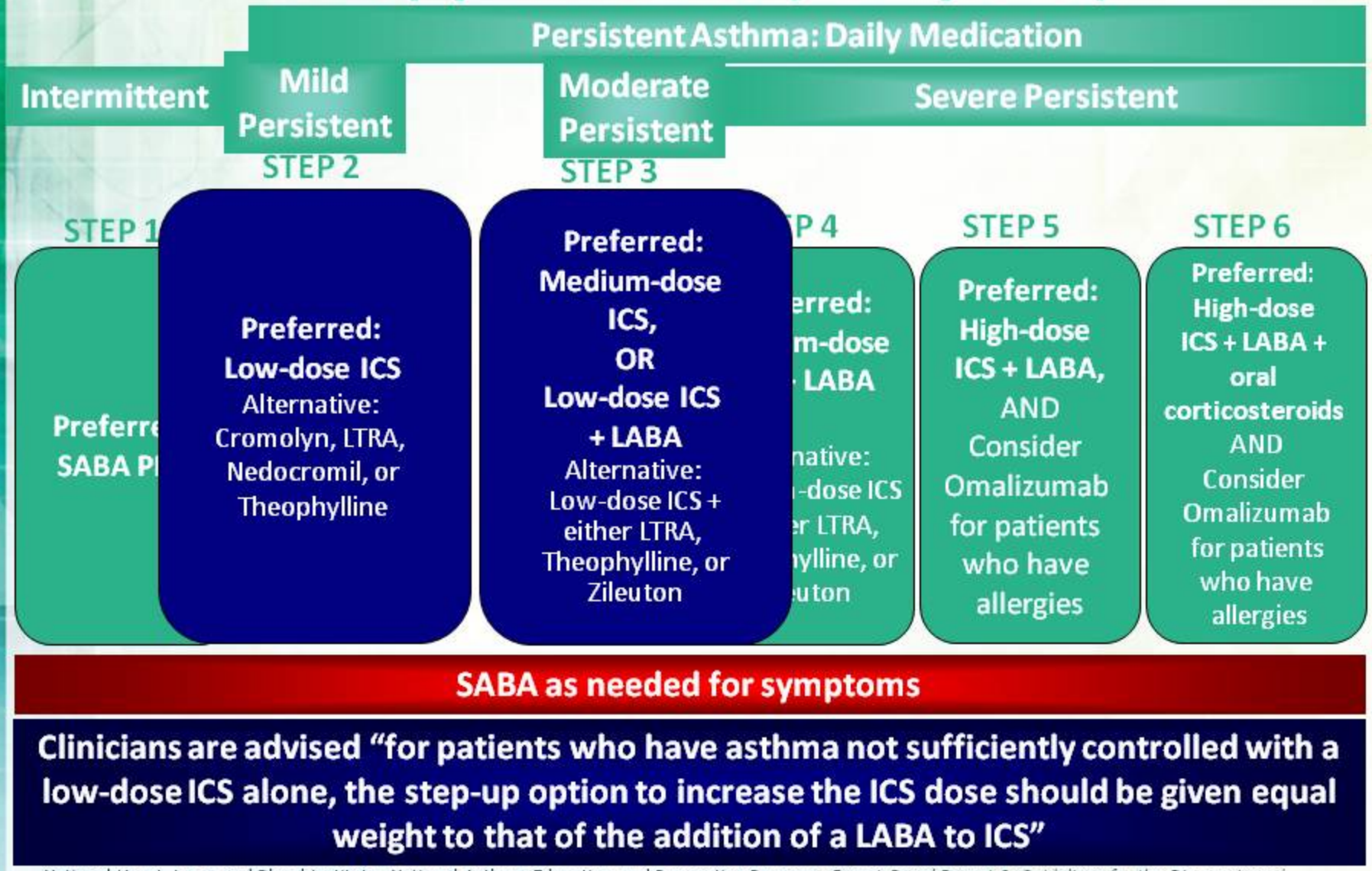
NIH Asthma Guidelines for Initiation of Therapy in Adults (≥12 years)



Clinicians are advised "for patients who have asthma not sufficiently controlled with a low-dose ICS alone, the step-up option to increase the ICS dose should be given equal weight to that of the addition of a LABA to ICS"

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007*. National Institutes of Health; August 28, 2007.

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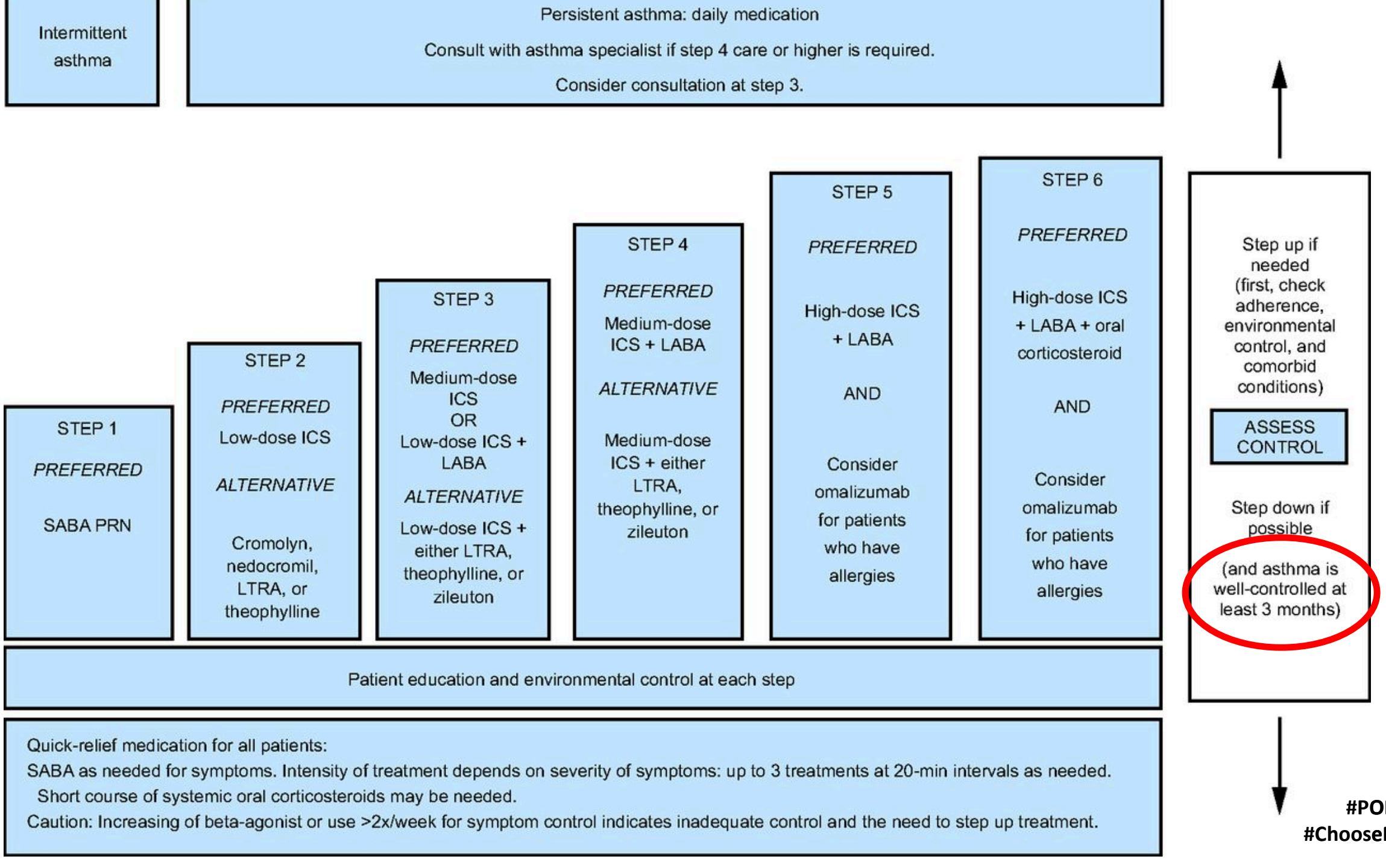

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Anti-IgE –Omalizumab(Xolair) in Severe Asthma

- Binds and down regulates free IgE
- Belgian Registry: 53% of pts…↑IgE levels
- First Biologic approved in the US: 2003
- ↓Asthma exacerbation by 38%
- ↓ ER visits by 47%
- ↓Systemic steroids by 43%
- Blunted the spring/fall spike exacerbation
- The higher the IgE level, the more effective the drug

Busse, W. Current Med Res Opin 2007;23(10):2379.
Braunstahl G, Respir. Med 2013; 107(8):1141

Subcutaneous XOLAIR doses every 2 or 4 weeks* for patients 12 years of age and older with asthma

Pretreatment serum IgE (IU/mL)	Dosing freq.	Body weight			
		Pounds			
		66-132 lb	>132-154 lb	>154-198 lb	>198-330 lb
		Kilograms			
		30-60 kg	>60-70 kg	>70-90 kg	>90-150 kg
		Dose (mg)			
≥30-100	Every 4 weeks	150	150	150	300
>100-200		300	300	300	225
>200-300		300	225	225	300
>300-400	Every 2 weeks	225	225	300	
>400-500		300	300	375	
>500-600		300	375	Insufficient data to recommend a dose	
>600-700		375			

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

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New ATS/ERS Task Force recommendations in poorly controlled asthmatics with severe asthma

- Anti-IL5/anti IL-5R in eosinophilic asthma
- Use blood eosinophil count≥150/µL
- Consider if Eos≥260/µL and FeNO≥19.5 for greater response for Anti-IgE therapy
- Inhaled Ipratropium despite GINA 4-5 or NAEPP Step 5 therapies
- Chronic macrolide therapy for NAEPP Step 5/GINA step 4-5 irrespective of asthma phenotype
- Anti-IL4/13 use in severe eosinophilic asthma, severe corticosteroid asthma regardless of blood eosinophil levels

FDA-approved Anti-IL-5 and –IL-4/IL-13 Therapies

Agent	Patients	Effects on Annualized Exacerbation Rate vs. Placebo	FDA-Approved Dosage
Mepolizumab NUCALA (Anti-IL-5)	N=576 Eos≥150/ µL at screening or ≥300/µL within the prior year	↓53%, P<0.001	SC:100 mg q 4w
Reslizumab CINQAIR (Anti-IL-5)	N=953 2 identical randomized trials Eos≥400/µL	↓50%, 59%; P<0.0001	IV infusion: 3 mg/kg q4w
Benralizumab FASERNA (Anti-IL-5 receptor)	N=1205 and N=1306; 2 identical trials No Eos criteria Population analysis: Eos≥300/µL	Primary Populations analysis: ↓45%, q4w ↓51% q8w; P<0.0001 Both comparisons: ↓46% q4w; P=0.002 ↓38% q8w; P=0.019	SC: 30 mg q4w x 3 doses Then 30 mg q8w
Dupilumab DUPIXENT (Anti-IL-4/IL-13)	N=1902 No eosinophil criteria	Full study population: ↓48%, 200 mg, q4w ↓46%, 300 mg q2w vs placebo; P<0.001	SC: Initial dose of 400 mg, then 200mg q2w or initial dose of 600 mg, then 300mg q2w

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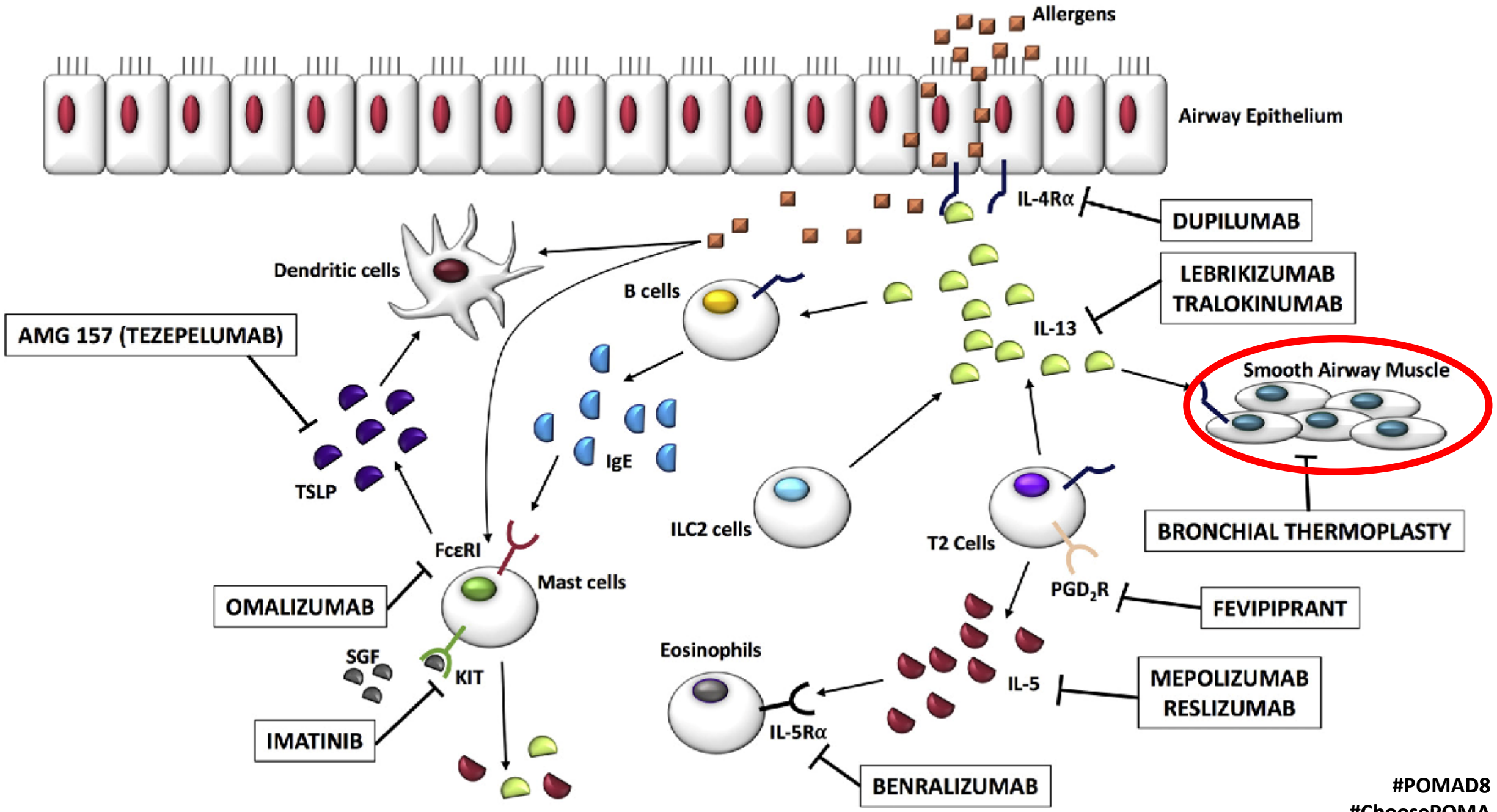

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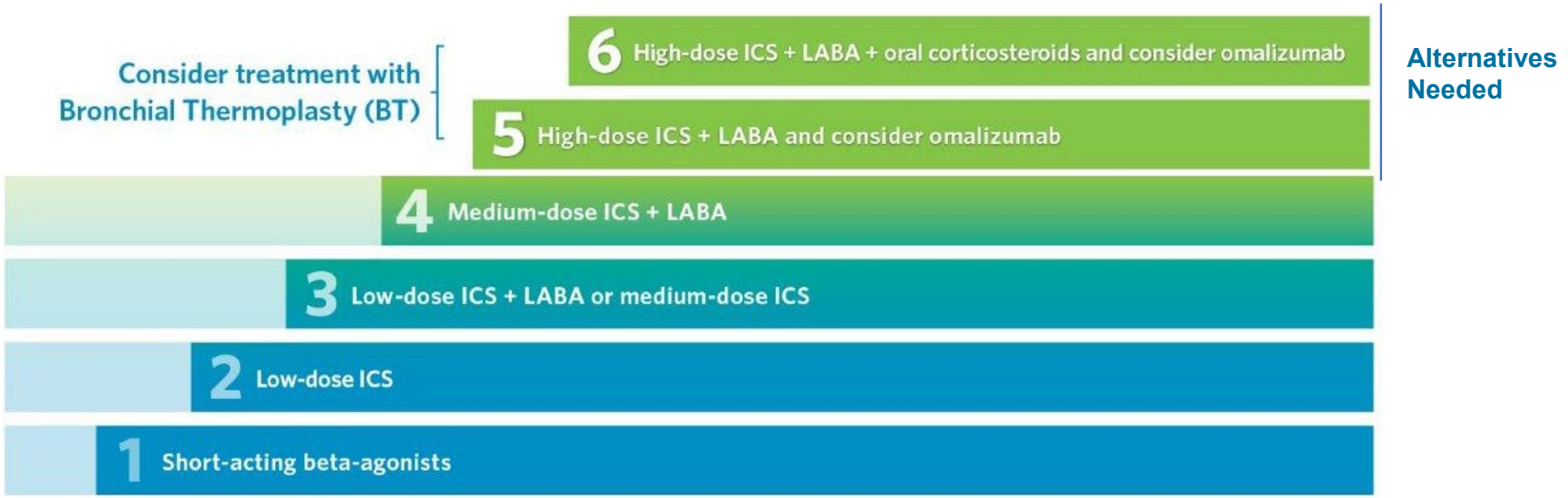
Challenges in Severe Asthma

- ASTHMA is a heterogeneous disease characterized by diverse symptom profiles and response to medications
- MEDICATIONS are ineffective in *some* patients, require adherence, and can have serious side effects
- Are patients avoiding asthma triggers?
- **SUBSET** of patients remain symptomatic and experience **quality of life limitations** despite standard of care medications
- Patients with SEVERE ASTHMA experience *higher rates of asthma exacerbations, increased morbidity and disproportionate use of healthcare resources: cost*

More Treatment **Options** Needed When Medications Aren't Working



Current stepwise approach for asthma management in patients 12 years of age or older.
Adapted from National Asthma Education and Prevention Program (NAEPP) Guidelines. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute, NIH Publication No. 07-4051, Revised August 2007.

BT is indicated for patients 18 years and older.

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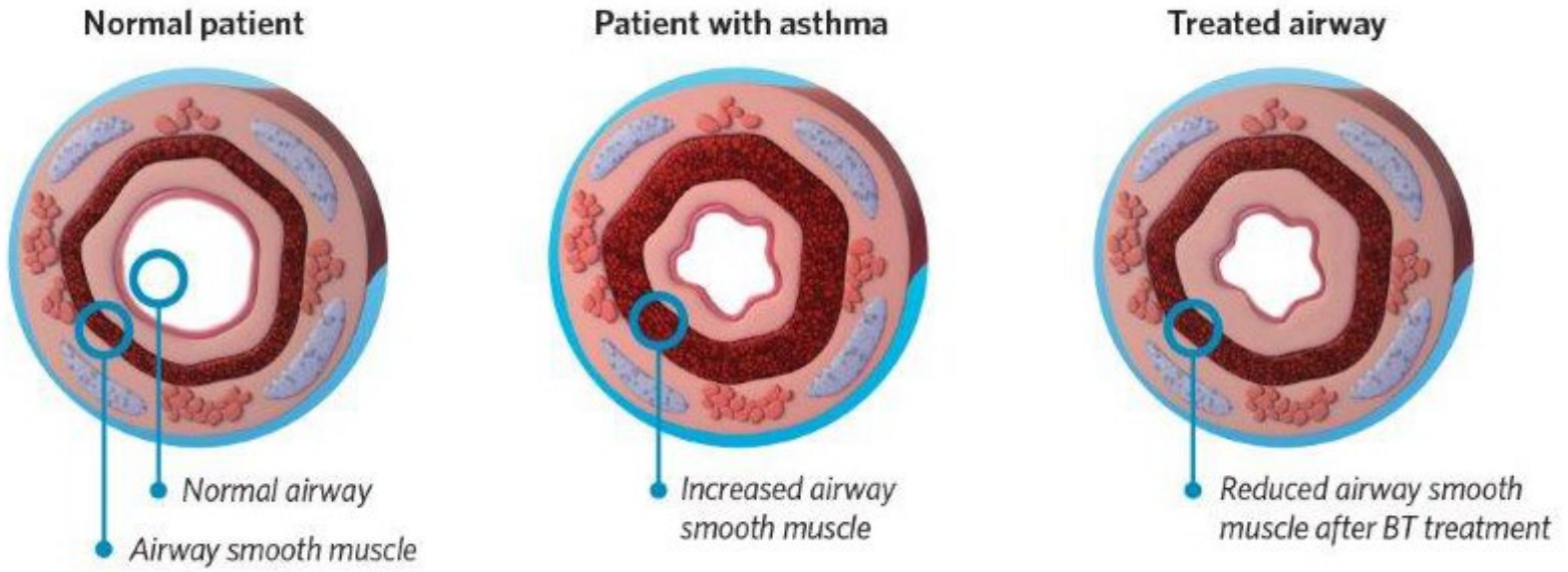
What is Bronchial Thermoplasty?

- **Safe, outpatient bronchoscopic** procedure:
  - Delivers controlled THERMAL energy to the airway walls in the lungs
  - Reduces excess airway smooth muscle, which limits the muscle's ability to constrict the airways (asthma exacerbations)
  - Indicated for treatment of moderate-severe asthma not well controlled with ICS and LABA
- Demonstrated to **increase asthma control** and **improve asthma-related quality of life** in patients with severe asthma[1,2]
- **Complementary treatment** to current asthma reliever and controller medications - not a cure or replacement for current asthma medications

1. Castro, Am J Respir Crit Care Med. 2010;181(2):116-24
2. Castro M, et al. Ann Allergy Asthma Immunol. 2011 Jul;107(1):65-70

Bronchial Thermoplasty – Reduces Excess ASM



Reduce Airway Smooth Muscle (ASM) → Reduce Bronchoconstriction → **Reduce Asthma Exacerbations** → **Improve Asthma Quality of Life**

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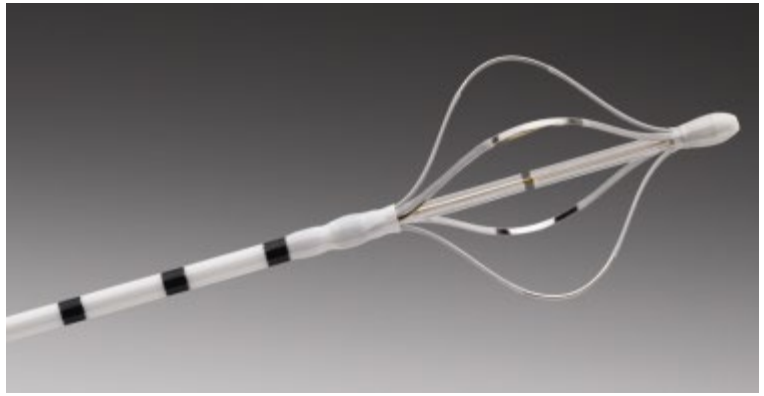
The Alair® Bronchial Thermoplasty System

- **Alair Catheter** – a flexible tube with an expandable wire array at the tip (introduced into the lungs through a standard bronchoscope)



- **Alair Radiofrequency (RF) Controller** – supplies energy via the Catheter to heat the airway wall

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BT Procedure

- Moderate-Severe, persistent refractory asthma
- 3 sessions≈1 hr each
- Ablation of airway smooth muscle(as small as 3 mm diameter) via radiofrequency energy @65^{o} C
- FDA approved(2010)
- CMS approved

BT, Delivered by the Alair™ System

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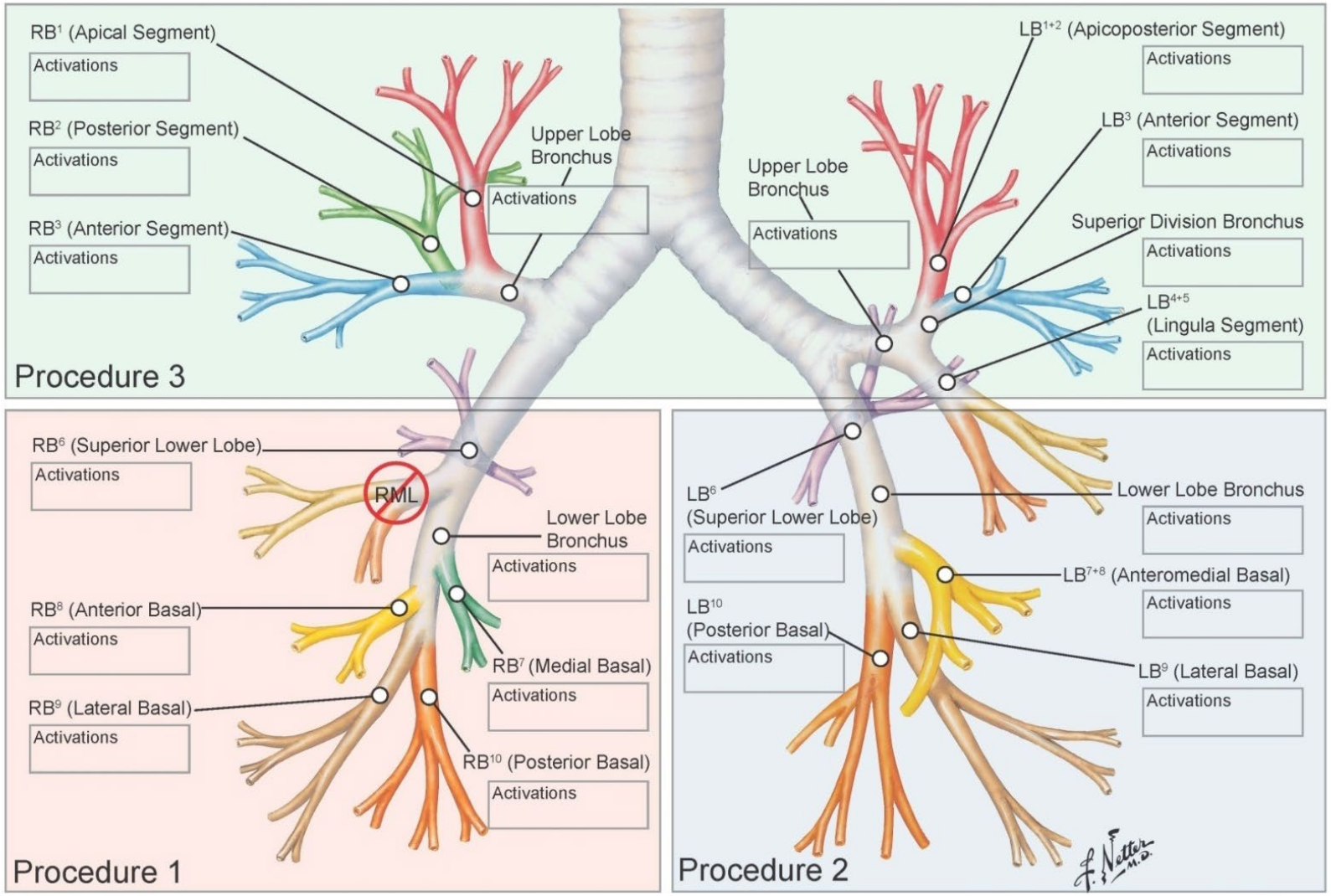
3 Different BT Procedures 3 weeks apart



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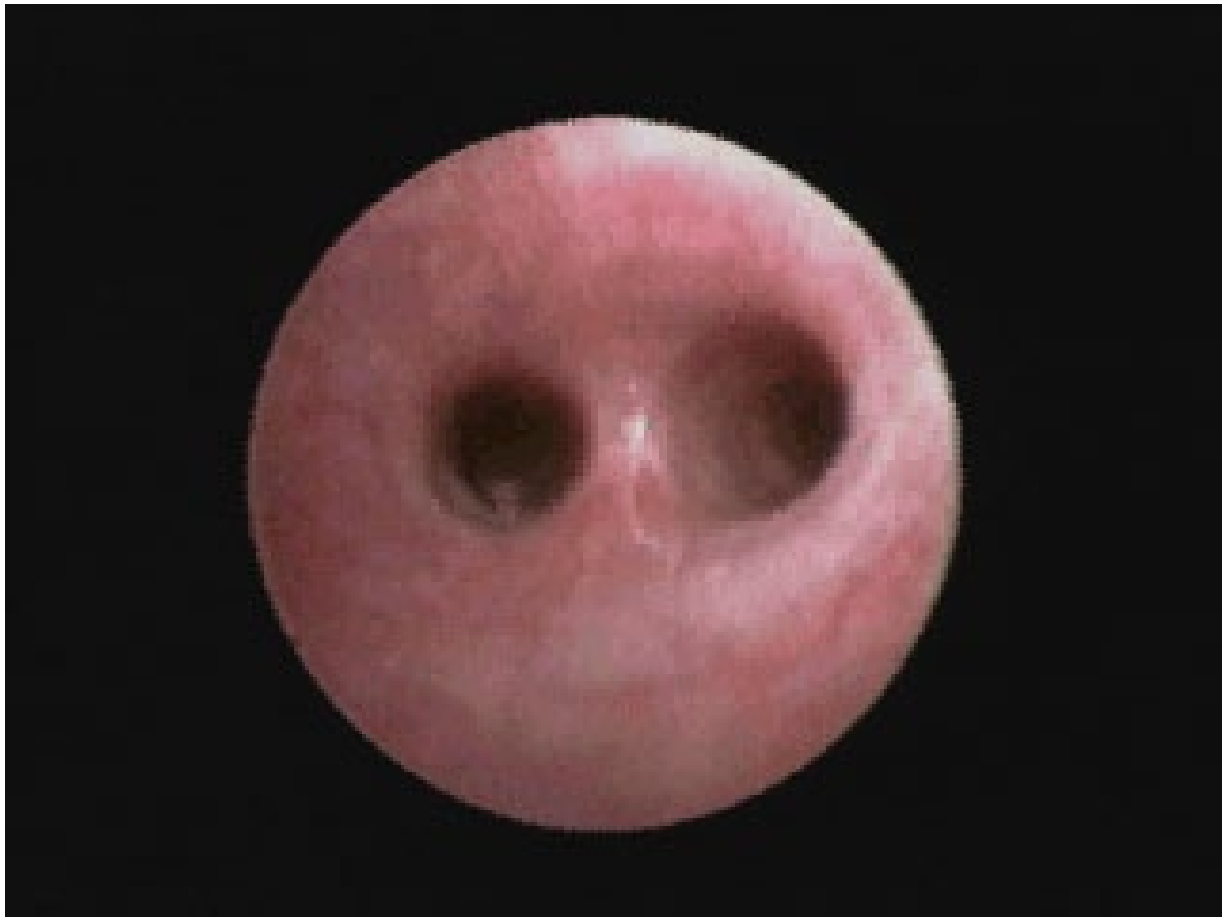
Bronchoscopic View of Local Methacholine Challenge

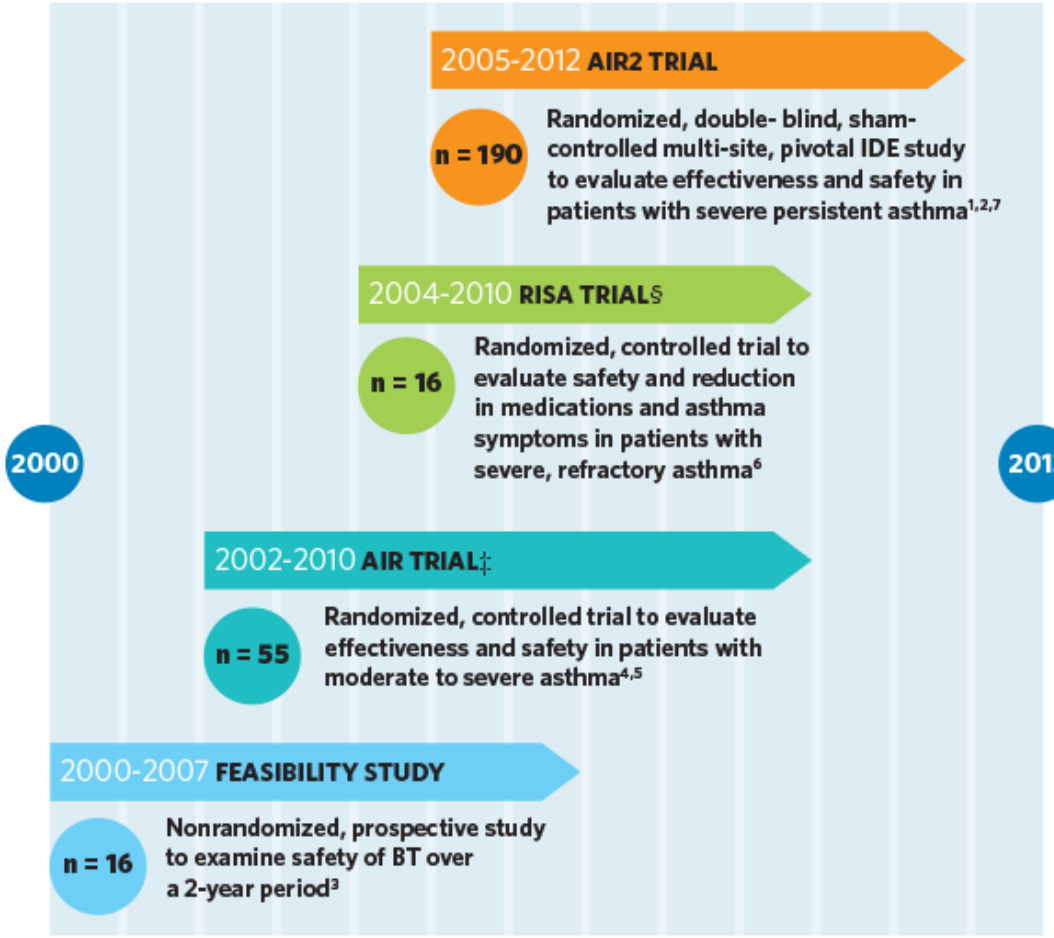


BT-treated airway on left

Cox et al. ERJ 2004

Evolution of Bronchial Thermoplasty – A Rigorous Clinical Approach

13+ years of clinical experience



- 13+ years of clinical research and experience
- 4 clinical studies in patients with asthma, all with 5 years of follow-up
- 3 randomized, controlled, clinical studies including the AIR2 Trial: double-blinded, sham-controlled pivotal trial for FDA approval in treatment of severe asthma
- FDA approved April 2010

‡Asthma Intervention Research (AIR)
§Research in Severe Asthma (RISA)

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5-Year Safety and Effectiveness Data

Study Title	Study Description	Related Publications	No. of Patients	Key Findings
AIR2 Trial 5-Year Extension Study (Post Approval Study)	Long-term durability of effectiveness (in BT-treated patients in the AIR2 Trial)	Wechsler et al., JACI 2013 Castro et al., AnnAAI 2011	181 BT	• Long-term effectiveness maintained, demonstrated by reduction in the percentage of patients with severe exacerbations maintained out to 5 years • Reduction in ER visits maintained out to 5 years • Stable long term safety profile (out to 5 years)
AIR2 Trial	Randomized, double-blind, sham-controlled trial to evaluate effectiveness and safety in patients with severe asthma	Castro et al., AJRCCM 2010	196 BT, 101 Sham	• 32% reduction in severe exacerbations • 84% reduction in ER visits • 66% reduction in days lost from work/school/other daily activities due to asthma symptoms • Stable long term safety profile (1 year follow-up)
AIR Trial	Randomized, controlled (to standard-of-care) trial to evaluate efficacy and safety in patients with moderate to severe asthma	Cox et al., NEJM 2007	56 BT, 56 Control	Study data were submitted to FDA as proof-of-principle and evidence of safety prior to beginning the pivotal AIR2 Trial.
AIR Trial Extension	Long-term (5 year) safety of Bronchial Thermoplasty (in BT treated patients in the AIR Trial)	Thomson et al., BMC Pulmonary Medicine 2011	45 BT	Study data were submitted to FDA as proof-of-principle and evidence of safety.
RISA Trial	Randomized, controlled (to standard-of-care) trial to evaluate safety in patients with severe, refractory asthma	Pavord et al., AJRCCM 2007	15 BT, 17 Control	• Stable, long-term safety profile (1 year follow-up) • Improvements in measures of asthma control • Strong suggestion of reduction in OCS use
RISA Trial Extension	Long-term safety (5 year) of Bronchial Thermoplasty (in BT-treated patients in the RISA Trial)	Pavord et al., AnnAAI 2013	14 BT	• Stable long-term safety profile out to 5 years
Feasibility Study	Safety study in patients with mild to severe asthma; Patient satisfaction survey	Cox et al., AJRCCM 2006	16 BT	Study data were submitted to FDA as proof-of-principle and evidence of safety prior to beginning the pivotal AIR2 Trial.

AIR2 Trial

AIR Trial

RISA Trial

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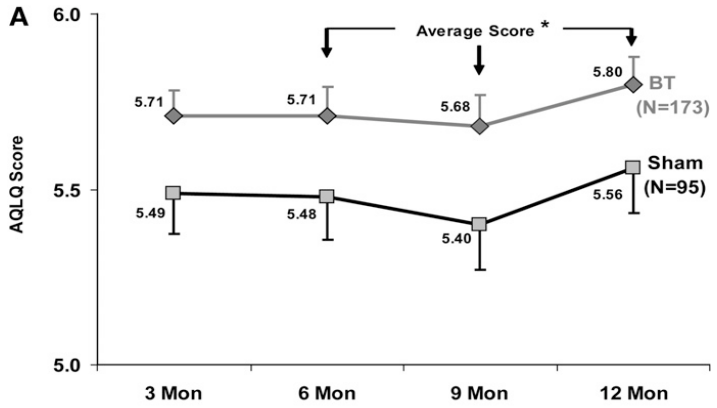
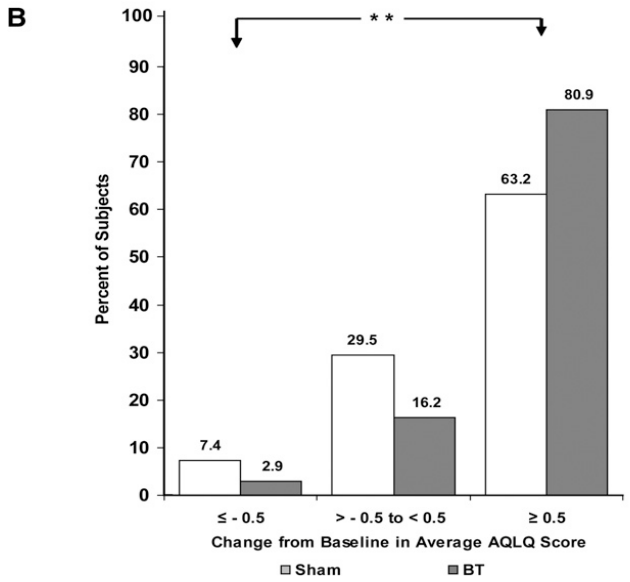
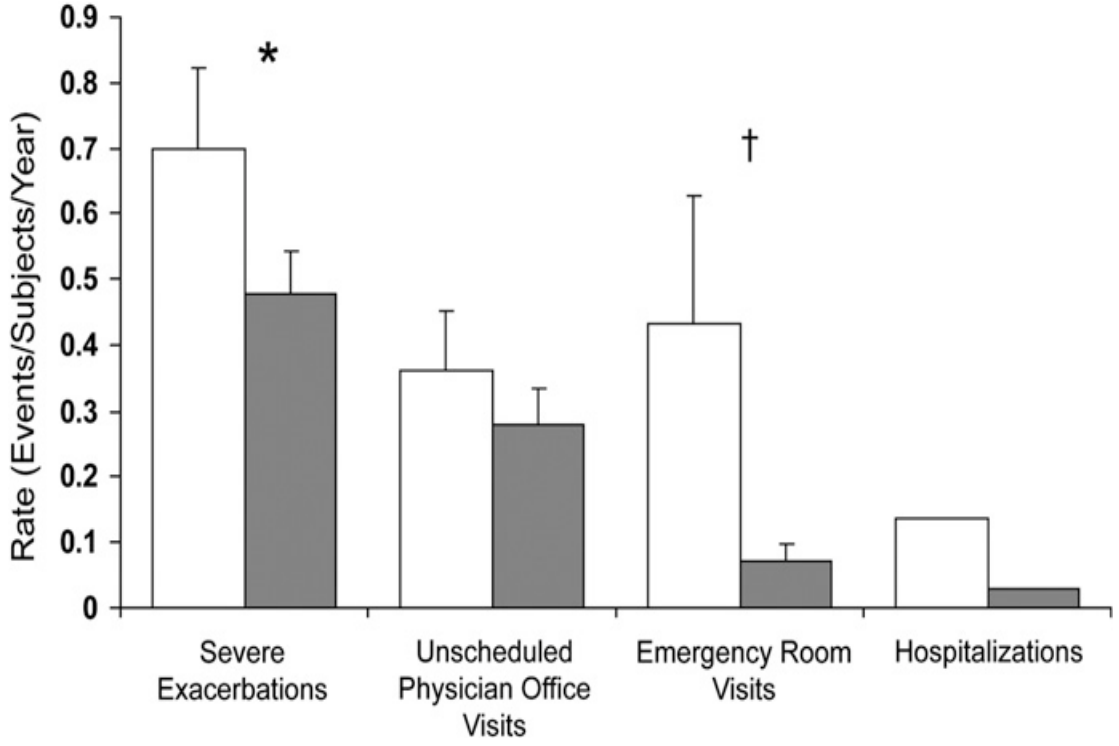
AQLQ--Key Data from AIR2







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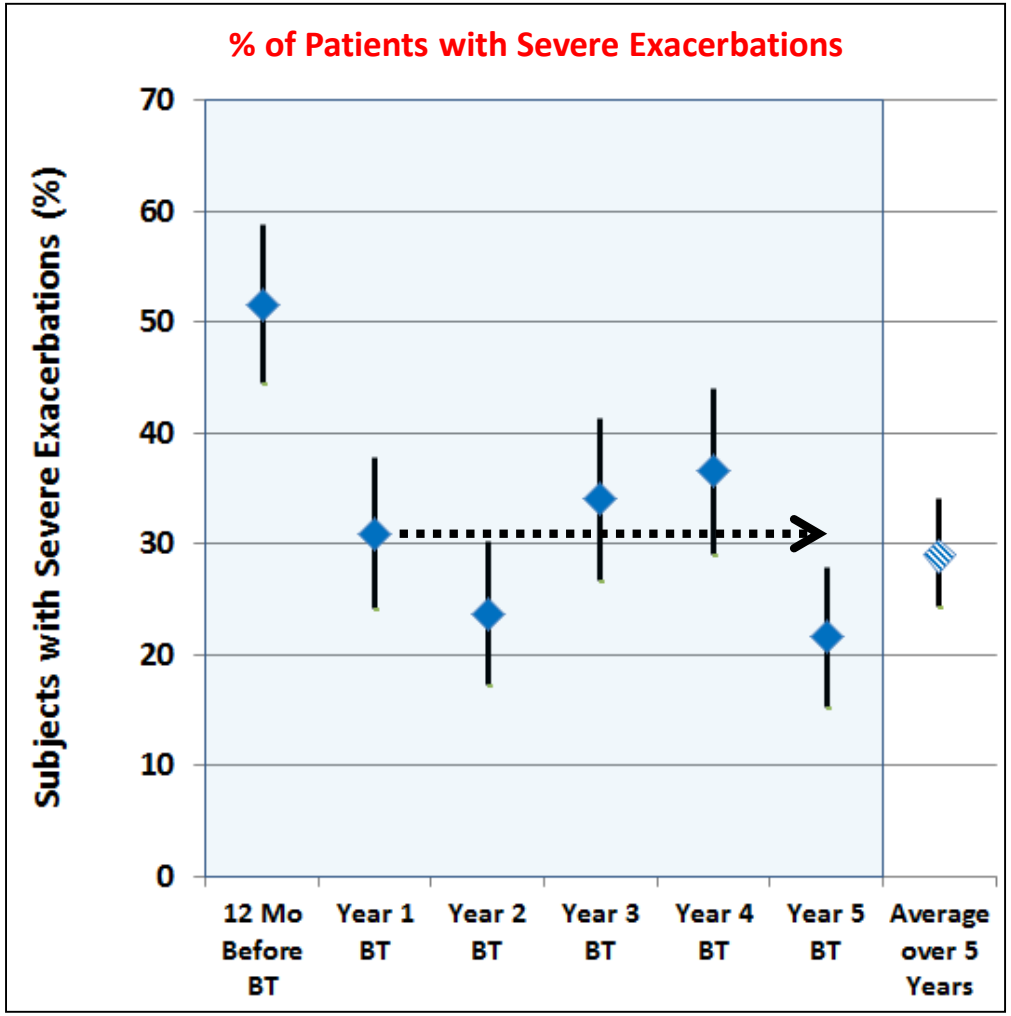
AIR2 Extension Study
Primary Endpoint Achieved



- Compared with Year 1, the percentage of BT patients experiencing severe exacerbations at Years 2-5 met the established non-inferiority margin

Wechsler ME, et al; for the Asthma Intervention Research 2 Trial Study Group. *J Allergy Clin Immunol.* 2013 Dec;132(6):1295-1302

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Established Long-Term Effectiveness and Safety out to 5 Years[1]

The AIR2 Trial 5-Year Extension Study evaluated the sustained effectiveness of BT beyond 1 year, and the safety of BT out to 5 years in BT-treated patients from the AIR2 Trial.

- **Reduction in severe asthma exacerbations requiring systemic corticosteroids** seen at 1 year was maintained out to 5 years
- **Reduction in ER visits for respiratory symptoms** seen at 1 year was maintained out to 5 years
- **Long-term safety** maintained over 5 years

1. Wechsler ME, et al; for the Asthma Intervention Research 2 Trial Study Group. *J Allergy Clin Immunol.* 2013 Aug 30. doi:pii: S0091-6749(13)01268-2. 10.1016/j.jaci.2013.08.009. [Epub ahead of print]

OUR BT DATA: AGH, DUBOIS, ERIE

DEMOGRAPHICS	
No. of subjects	34
Sex - no. (%}	
Male	10 (29)
Female	24 (71)
Age – Yr.	
Average	49
Min	25
Max	71
Race or ethnic group - no. (%)	
White	31(91)
Black	2 (5.8)
Hispanic	1 (2.9)
Weight lbs /BMI	
Average	193 (31.1)
Min	135 (21.6)
Max	360 (51.4)

BASELINE CLINICAL CHARACTERISTICS	AVERAGE
PEFR	406
Pre-bronchodilator FEV_1 %	83%
FeNO	32
AQLQ Score	3.57
ACT Score	14
ED Visits	2.15
Unscheduled Outpatient Visits	2.42
Hospitalization	1.76
Systemic Steroid Bursts	4.68
Days Lost From Daily Activities	67.13
Days Lost Of Work/School	18.64

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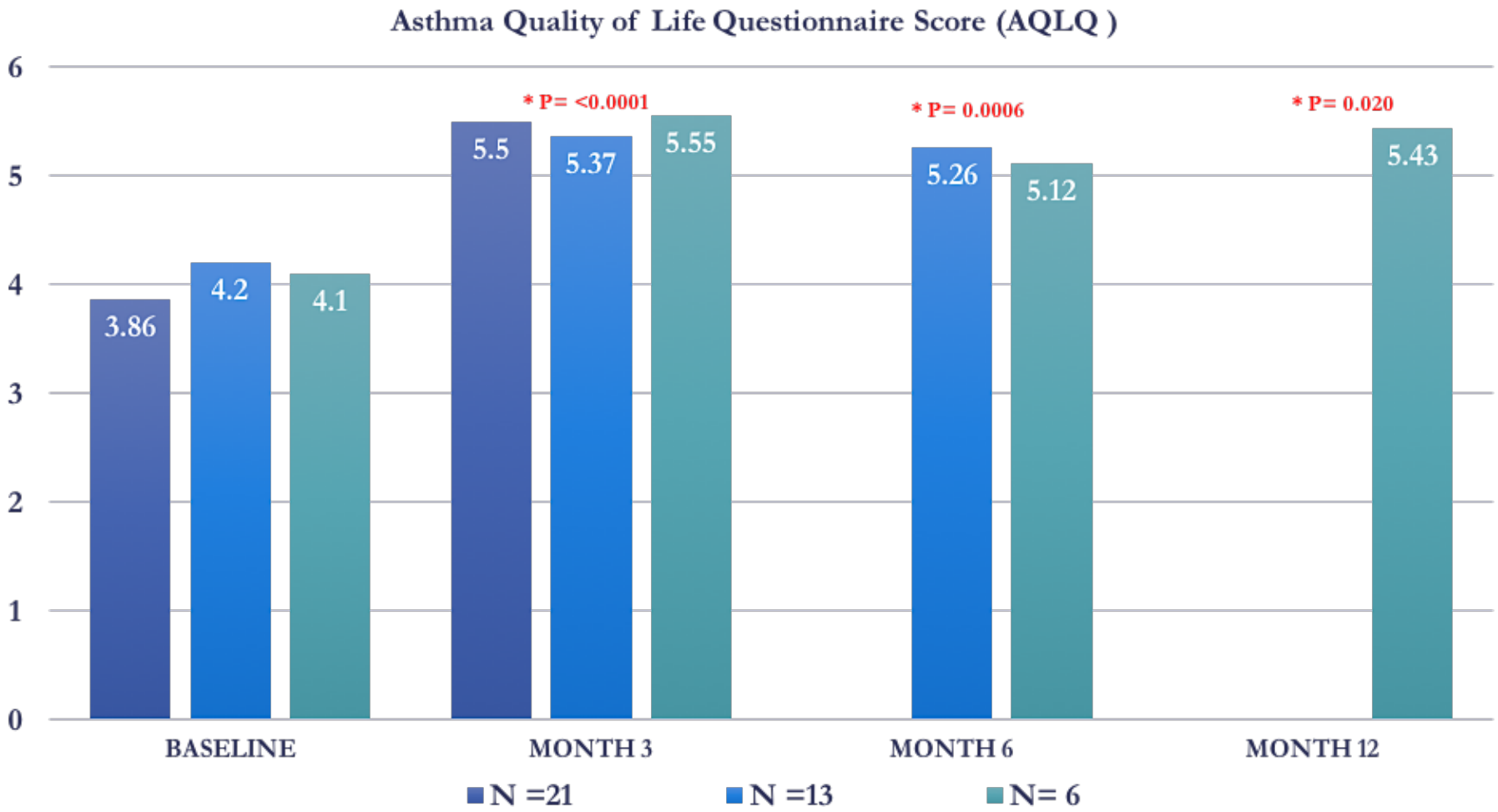

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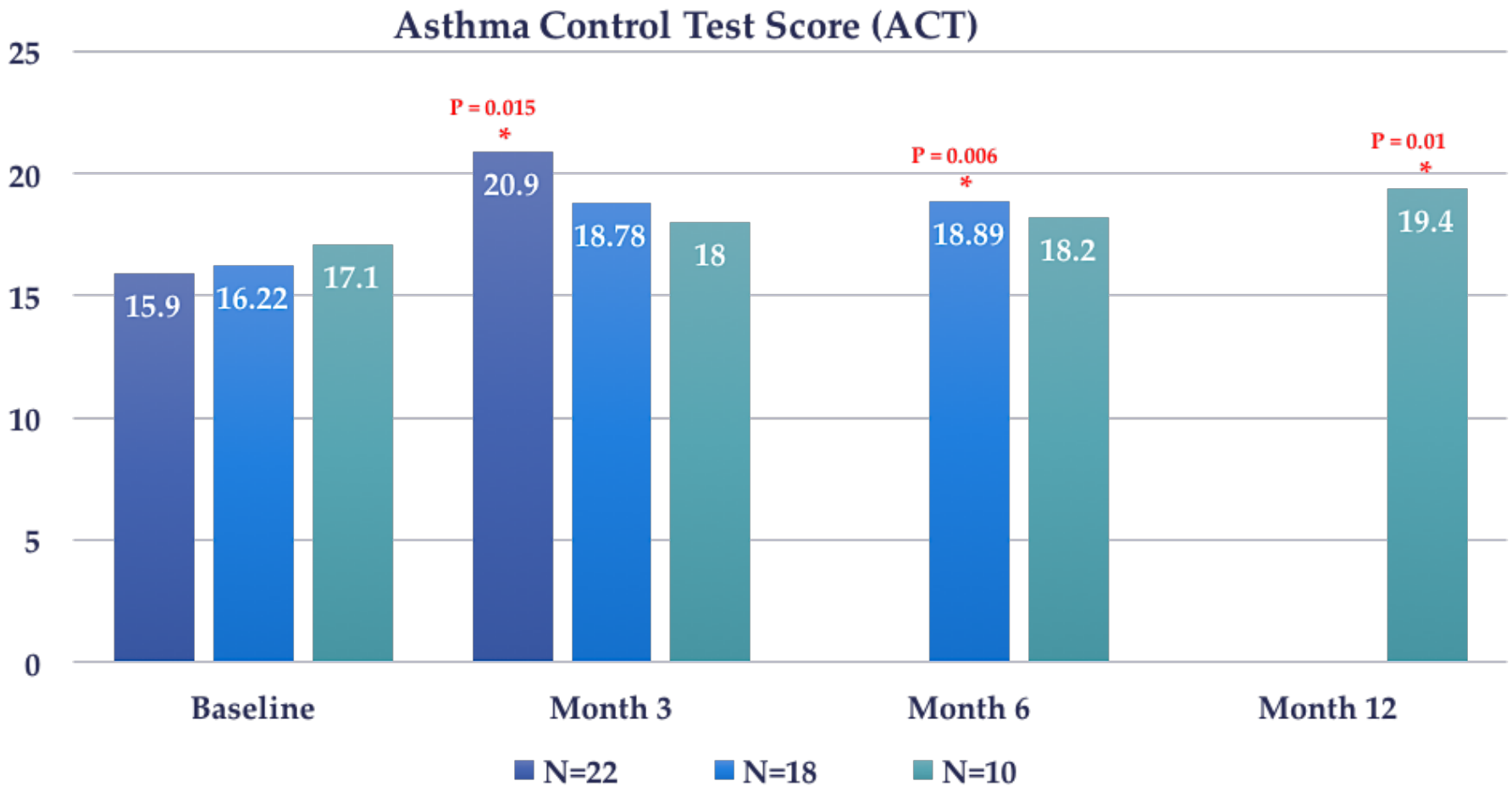

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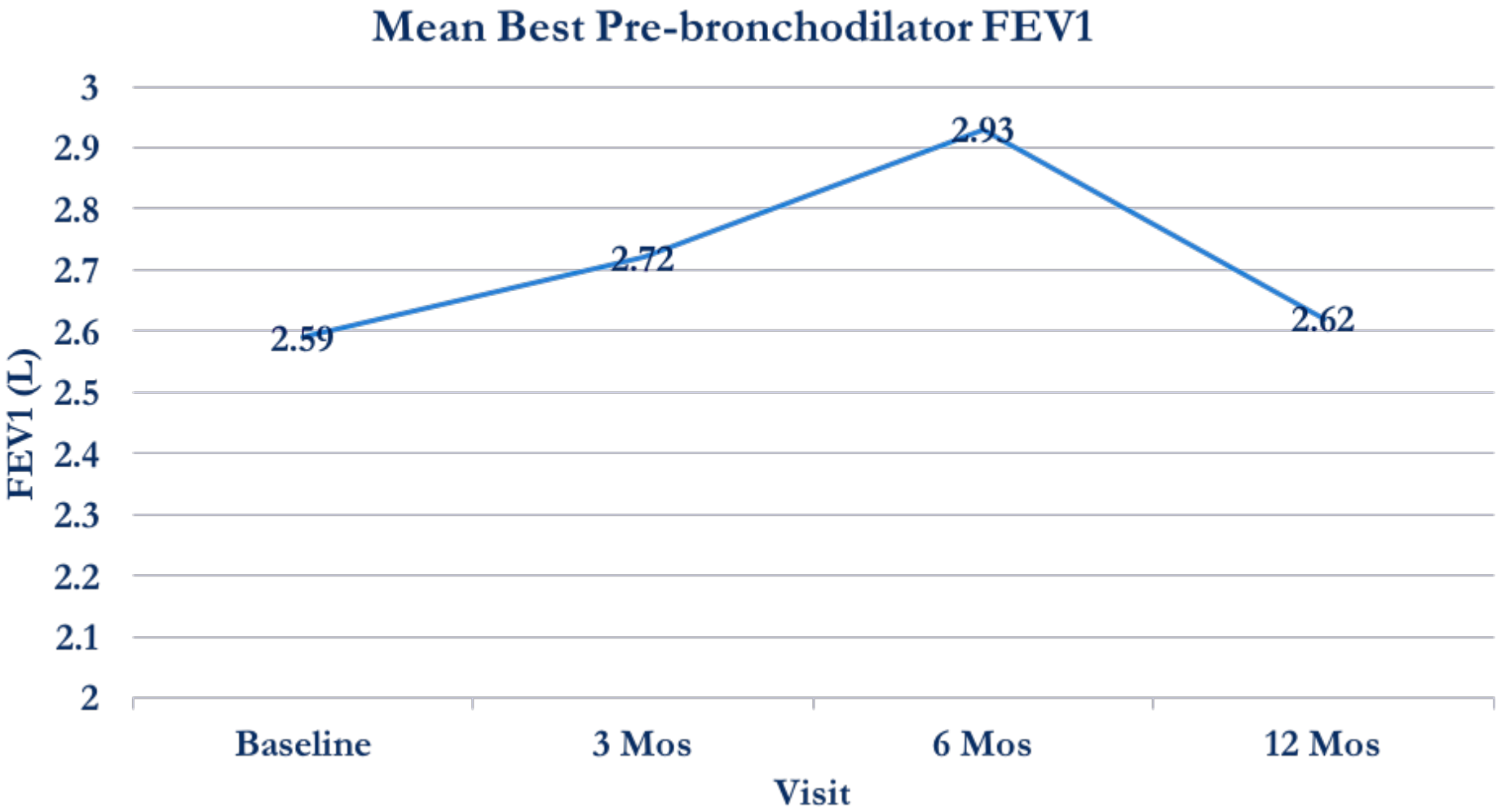

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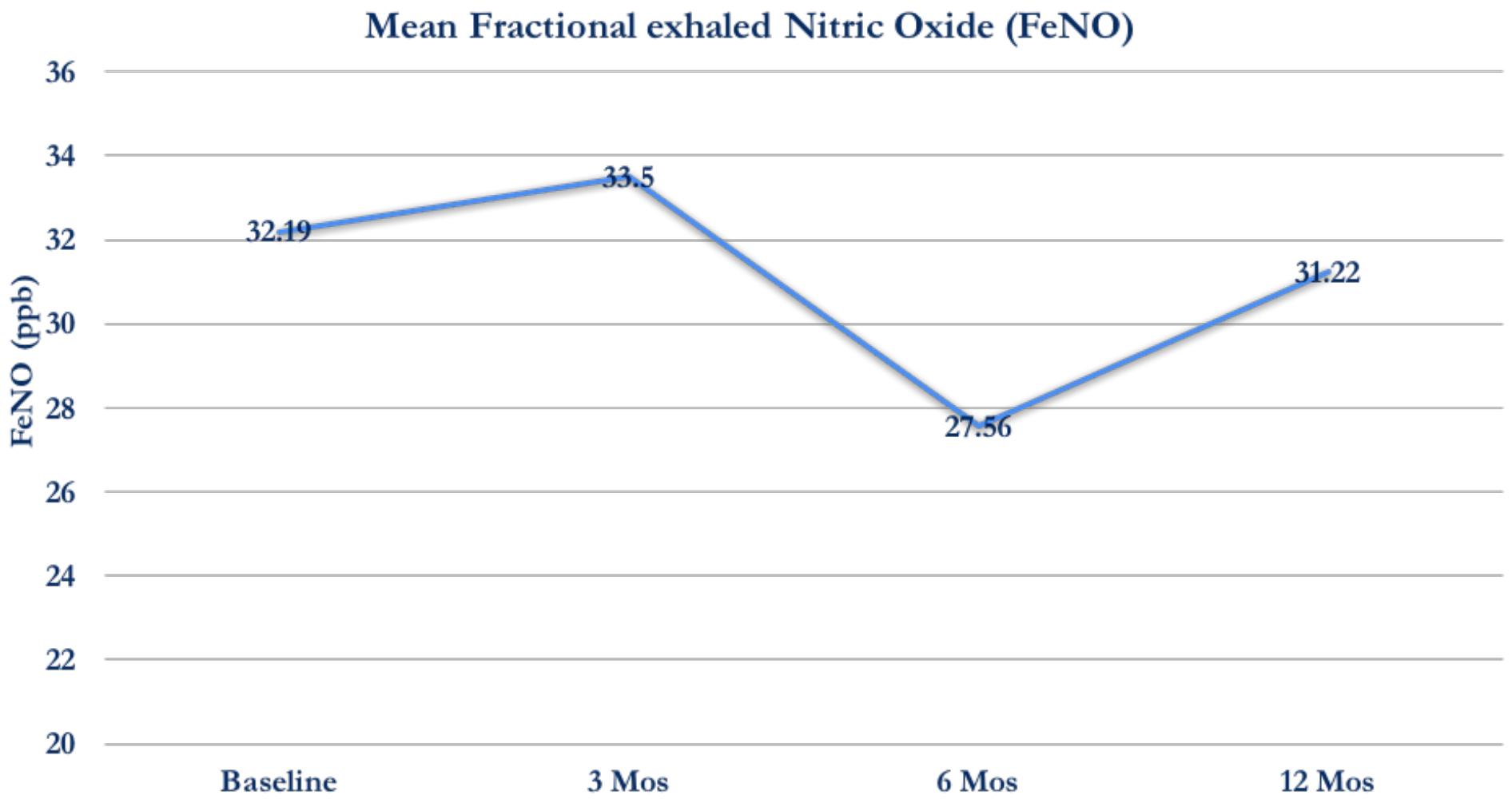

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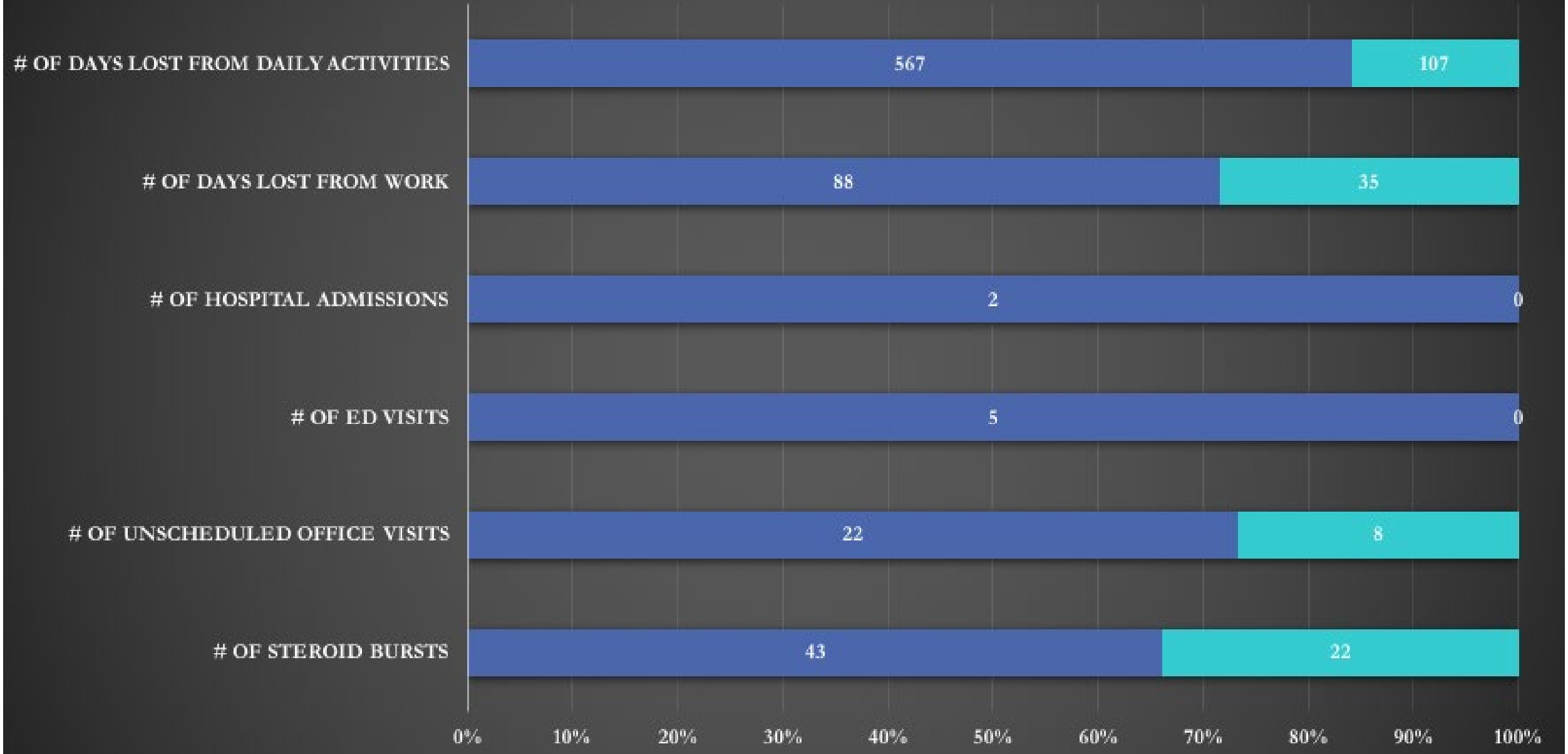
SECONDARY OUTCOMES - BASELINE VS 12 MONTHS POST - BT



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Pt case(From Dr. Hogarth/Univ of Chicago--By Permission)

- 33 yo M, full-term birth, non-smoker, with severe persistent asthma on **chronic** prednisone(lowest dose: 20 mg/day the last 3 yrs)
- On high dose ICS/LABA, plus additional nebulized steroids, montelukast, tiotropium, theophylline
- Baseline ACT: 6
- Blood work: ANCA neg, RAST neg, IgG normal, IgE normal. No Eos on peripheral smear
- Chest CT: Gas trapping, thick airways. No emphysema or nodules. No bronchiectasis

Pt case-cont'd

	Pre-Drug			Post-Drug		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
---- SPIROMETRY ----						
FVC (L)	4.22	4.69	89			
FEV1 (L)	3.80	3.74	101			
FEV1/FVC (%)	90	80	112			
FEF 25-75% (L/sec)	*6.19	4.11	*150			
FEF Max (L/sec)	8.64	8.92	96			

Methacholine was ++--at 2nd dose @0.25 mg/dl

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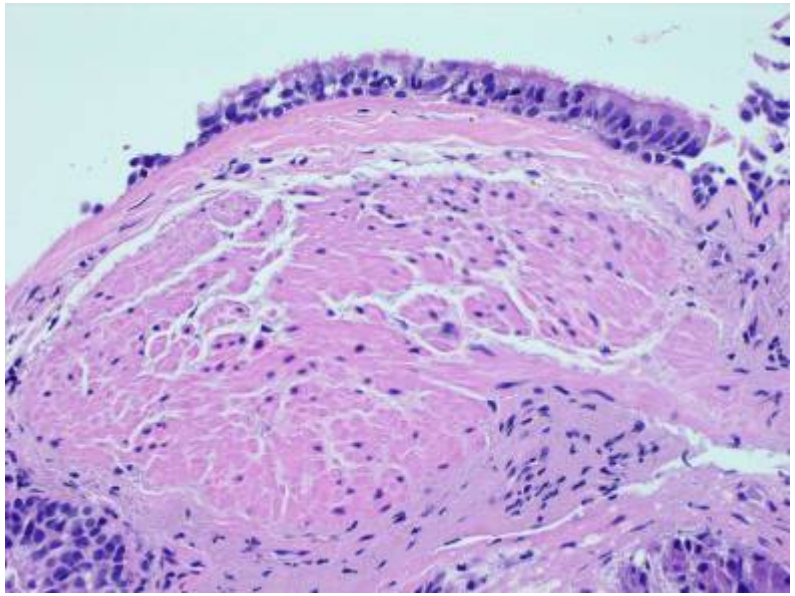
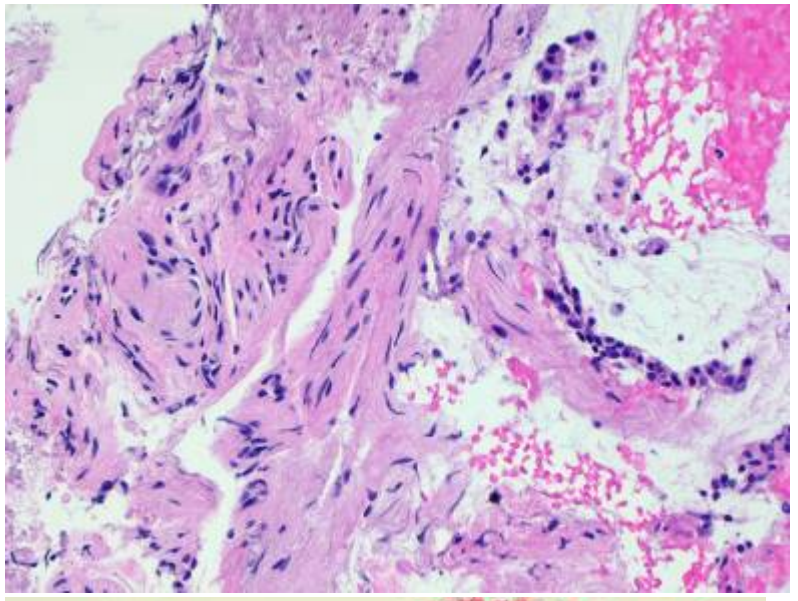
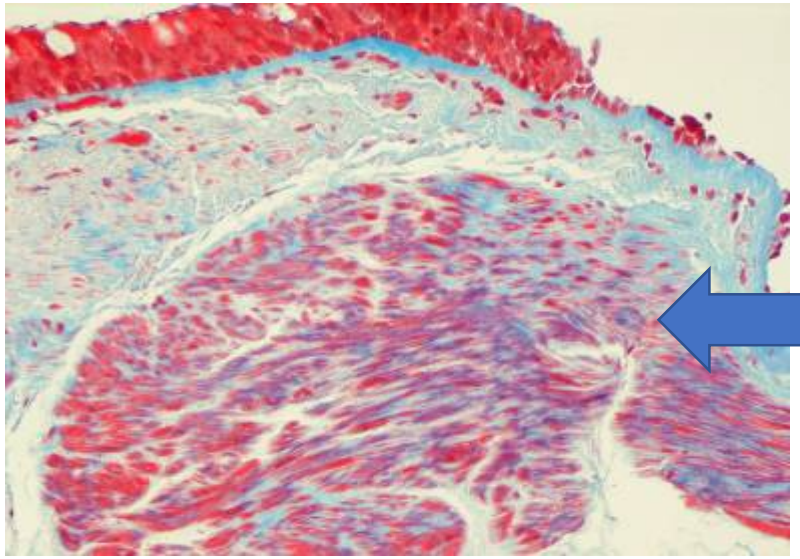
Pt case –cont'd
Chronic Therapy

Fluticasone/Salmeterol	Tiotropium
Prednisone	Theophylline
Montelukast	Budesonide nebs
Multiple antibiotic course	Metformin
Levalbuterol—frequent	Insulin
BIPAP-OSA	Alendronate
Sertraline	
Omeprazole	

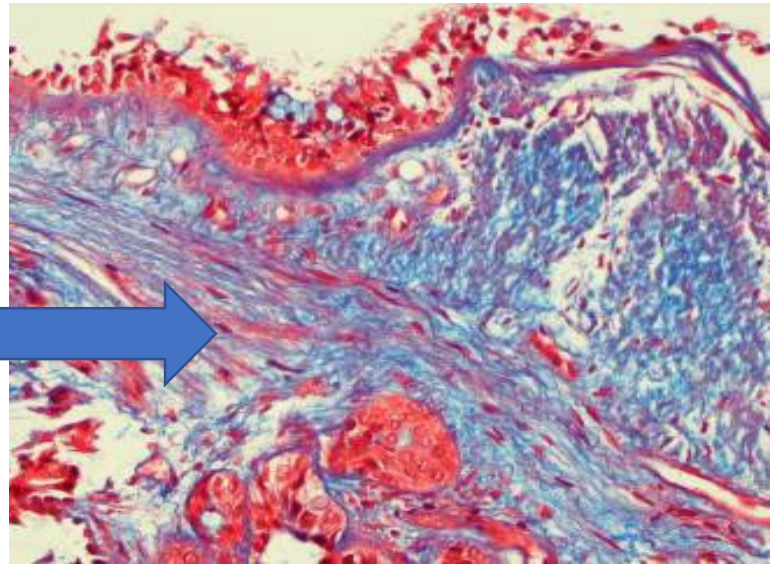
Airway Biopsies: Pre and Post BT







ASM



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45 mos-post BT

- “I feel like a I can do normal things”
- Most attacks are controlled by rescue inhaler
- 3 total overnight admissions to the hospital
- Off prednisone: Lost 32 lbs
- ACT score=32

COSTS AND INSURANCE REIMBURSEMENT

PROCEDURE				
TIME PERIOD	**#DAYS**	**HOSPITAL FEES**	**DOCTOR FEES**	**INSURANCE PAYMENTS**
12 mos Pre-BT	33	$177,963	$25,546	$141,421
12 mos POST-BT	1	$10,115	$1029	$4,604

Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations J. Clin Allergy and Immuno 2016

Marina Pretolani, PharmD, PhD*, Anders Bergqvist, PhD*, Gabriel Thabut, MD, PhD, Marie-Christine Dombret, MD, Dominique Knapp, MS, Fatima Hamidi, MS, Loubna Alavoine, MD, Camille Taillé, MD, PhD, Pascal Chanez, MD, PhD, Jonas S. Erjefält, PhD, Michel Aubier, MD

Background

The effectiveness of bronchial thermoplasty (BT) has been reported in patients with severe asthma, yet its effect on different bronchial structures remains unknown.

Objective

We sought to examine the effect of BT on bronchial structures and to explore the association with clinical outcome in patients with severe refractory asthma.

Methods

Bronchial biopsy specimens (n = 300) were collected from 15 patients with severe uncontrolled asthma before and 3 months after BT. Immunostained sections were assessed for airway smooth muscle (ASM) area, subepithelial basement membrane thickness, nerve fibers, and epithelial neuroendocrine cells. Histopathologic findings were correlated with clinical parameters.

Results

BT significantly improved asthma control and quality of life at both 3 and 12 months and decreased the numbers of severe exacerbations and the dose of oral corticosteroids. At 3 months, this clinical benefit was accompanied by a reduction in ASM area (median values before and after BT, respectively: 19.7% [25th-75th interquartile range (IQR), 15.9% to 22.4%] and 5.3% [25th-75th IQR], 3.5% to 10.1%, $P < .001$), subepithelial basement membrane thickening (4.4 μm [25th-75th IQR, 4.0-4.7 μm] and 3.9 μm [25th-75th IQR, 3.7-4.6 μm], $P = 0.02$), submucosal nerves (1.0 ‰ [25th-75th IQR, 0.7-1.3 ‰] immunoreactivity and 0.3 ‰ [25th-75th IQR, 0.1-0.5 ‰] immunoreactivity, $P < .001$), ASM-associated nerves (452.6 [25th-75th IQR, 196.0-811.2] immunoreactive pixels per mm^2 and 62.7 [25th-75th IQR, 0.0-230.3] immunoreactive pixels per mm^2, $P = .02$), and epithelial neuroendocrine cells (4.9/mm^2 [25th-75th IQR, 0-16.4/mm^2] and 0.0/mm^2 [25th-75th IQR, 0-0/mm^2], $P = .02$). Histopathologic parameters were associated based on Asthma Control Test scores, numbers of exacerbations, and visits to the emergency department (all $P \leq .02$) 3 and 12 months after BT.

Conclusion

BT is a treatment option in patients with severe therapy-refractory asthma that downregulates selectively structural abnormalities involved in airway narrowing and bronchial reactivity, particularly ASM, neuroendocrine epithelial cells, and bronchial nerve endings.

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Basic Science

- Downregulation of structural abnormalities
- At 3 months:
  - ↓↓↓ASM(Airway Smooth Muscle)
  - ↓Subepithelial BM thickening
  - ↓Submucosal nerve endings
  - ↓Neuroendocrine epithelial cells
  - ↓Immunoreactivity

Indications for BT

- Age 18 or older
- Non-smoker(accept <10 Pck-yrs)
- Moderate-Severe Persistent Asthma(>Step 4 asthma) treated aggressively for at least 6 months and has failed conventional therapy.
- Poorly controlled on standard aggressive care :
  - High Dose ICS and
  - LABA, TIOTROPIUM
  - Immunotherapy (Omalizumab or IL5, IL4/13 monoclonal Ab)
- FEV1<60% predicted??
- Document compliance with maximal therapy:
  - ICS for at least 3 consecutive months
  - LABA or Leukotriene inhibitor for at least 3 consecutive months
  - Therapy not effective or poorly tolerated with 2 or more exacerbations/yr
  - Taking or being considered for systemic steroids chronically

Summary &
Future Directions in Severe Asthma Care

- Standard Step Therapy—will continue with minor changes
- Classify and Sub-classify:
  - Type 2 asthma vs. Non-type 2 asthma
  - Neutrophilic
  - GERD contribution
  - Anxiety and depression
  - Obesity and OSA
  - ACO(Asthma and COPD overlap syndrome)
  - Sinusitis and Rhinosinusitis--?Nasal polyps
- Markers: Eos, IgE, FeNO, Interleukins, TSLP(Thymic Stromal lymphopoeitin) and others
- ROLE OF BRONCHIAL THERMOPLASTY—Complementary

  It is underutilized!

Thank you!

Questions?

#POMAD8
#ChoosePOMA