Bronchial Thermoplasty for Severe Asthma

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Outline

- Asthma the Disease
- Asthma Prevalence
- Medical Therapy
- BT for Severe Asthma

What is Asthma?

- Chronic condition of the airways:
  - Airway inflammation
  - Acute bronchoconstriction
- Symptoms are usually variable
- Airways become more sensitive and easily narrowed by certain factors called triggers
- Triggers can be different for different people, and can include allergens, irritants, exercise and infections
- When airways narrow, it may cause chest tightness, wheeze or cough, and it can make it harder to breathe
- May cause excess mucus production

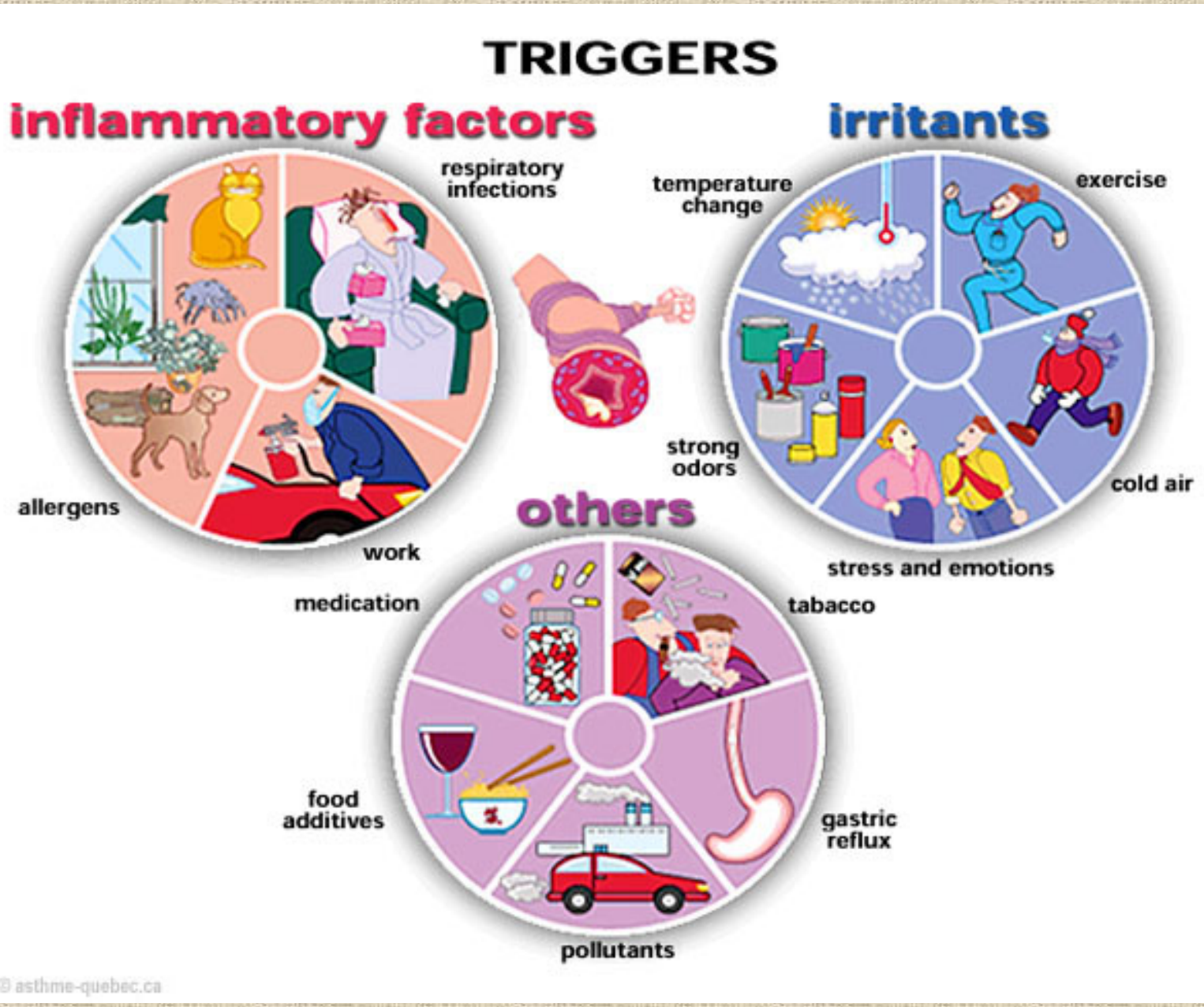
Two Main Types of Asthma

Allergic (or extrinsic) asthma (~60%)

- Immune system attacking allergen
- Allergic response - IgE antibody treats harmless substances as enemies

Non-Allergic (or intrinsic) asthma (~40%)

- Not triggered by an allergic reaction
- Immune system does not play a role
- Triggers may be anxiety, stress, cold air, dry air, hyperventilation, smoke, viruses or other irritants


TRIGGERS
inflammatory factors
respiratory infections
allergens
work
irritants
temperature change
exercise
strong odors
cold air
stress and emotions
others
medication
tabacco
food additives
gastric reflux
pollutants
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Mechanics of Asthma Attacks

Trigger

↓

Inflammation/swelling

+

Muscles that surround the airway constrict (bronchoconstriction), narrowing them

+

Production of excess mucus can plug airways

= /+

Long-term damage to airway walls prevents them from opening as widely as a non-asthmatic airway

↓

Asthma Attack!

What is Severe Asthma?

ERS/ATS 2014 Guidelines:

- **Severe asthma** is defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy."[1]

5%-10% of total asthma population estimated to have severe asthma[1]

ERS = European Respiratory Society
ATS = American Thoracic Society

1. Chung KF, et al. Eur Respir J. 2014 Feb;43(2):343-73.

Asthma: Prevalence, Morbidity and Mortality

Centers for Disease Control and Prevention National Center for Health Statistics, National Health Statistics Report: Asthma Prevalence, Health Care Use, and Mortality: United States, 2005–2009: http://www.cdc.gov/nchs/data/nhsr/nhsr032.pdf

Severe Asthma: Prevalence

300 Million People in the USA

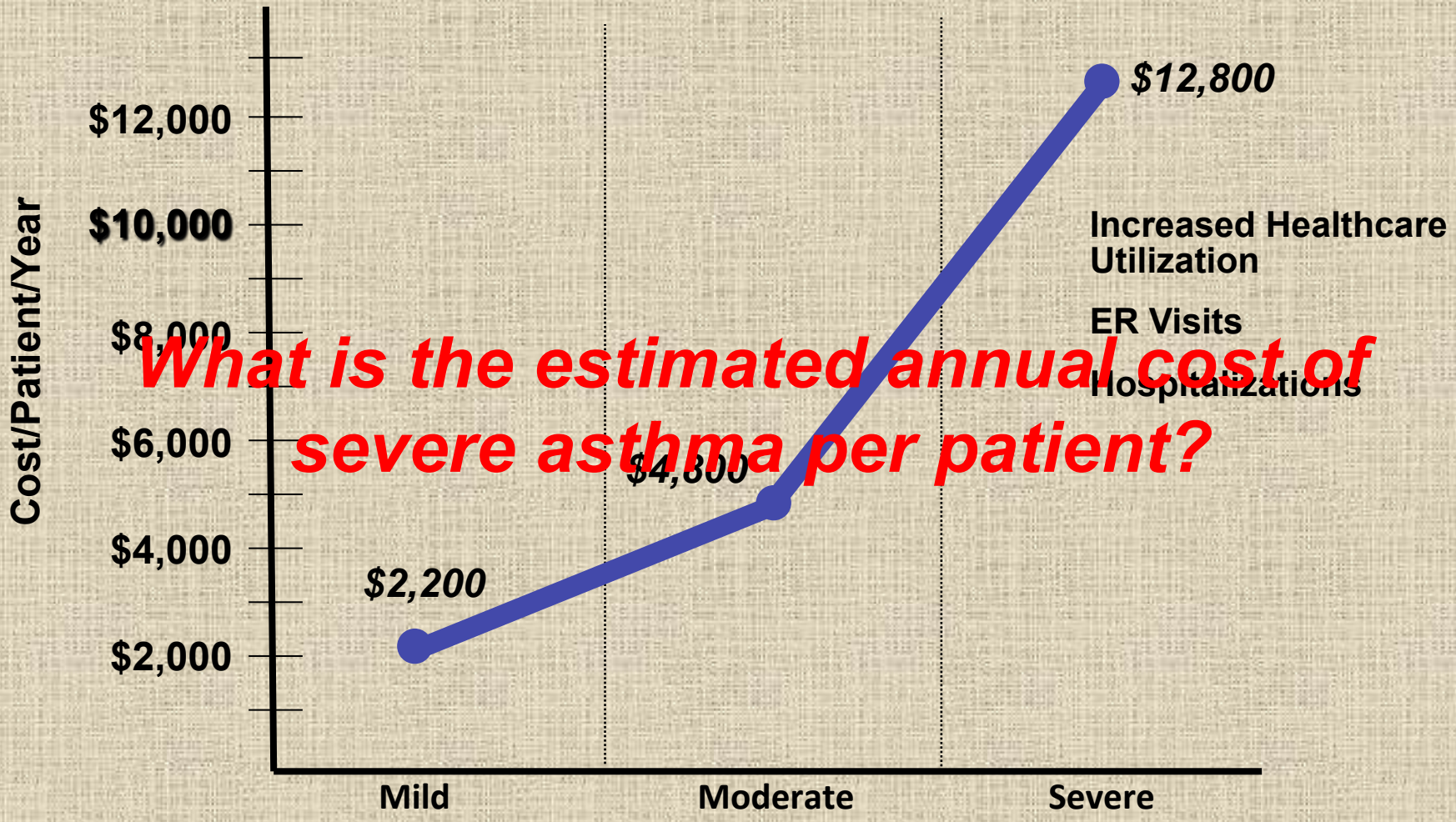
8.2% have asthma → **= 24.6 Million People**

70% are adults → **= 17.5 Million People**

10% have severe asthma → **= 1.7 Million People**

Centers for Disease Control and Prevention National Center for Health Statistics, National Health Statistics Report: Asthma Prevalence, Health Care Use, and Mortality: United States, 2005–2009: http://www.cdc.gov/nchs/data/nhsr/nhsr032.pdf

Annual Cost by Asthma Severity[1]

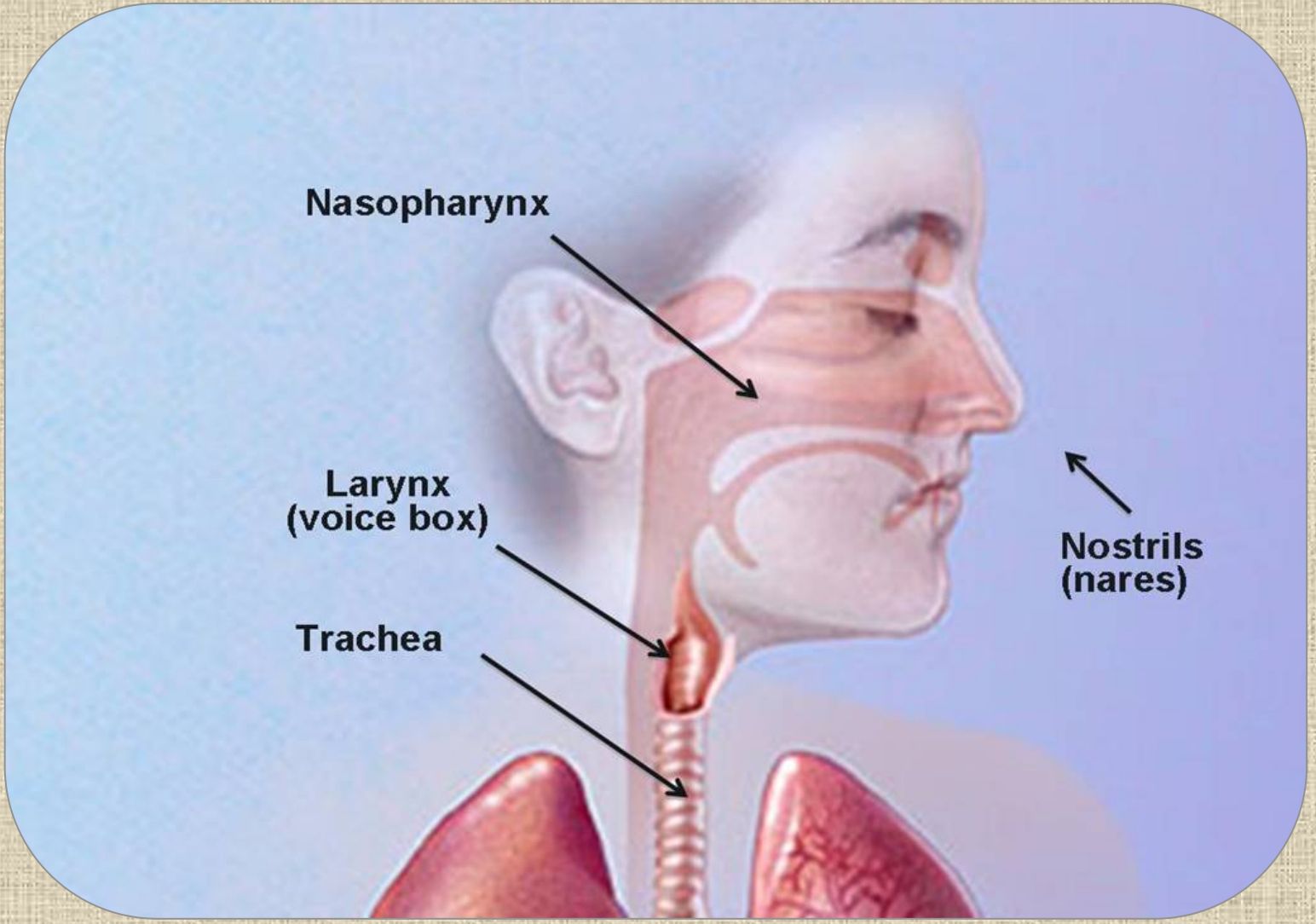


What is the estimated annual cost of severe asthma per patient?

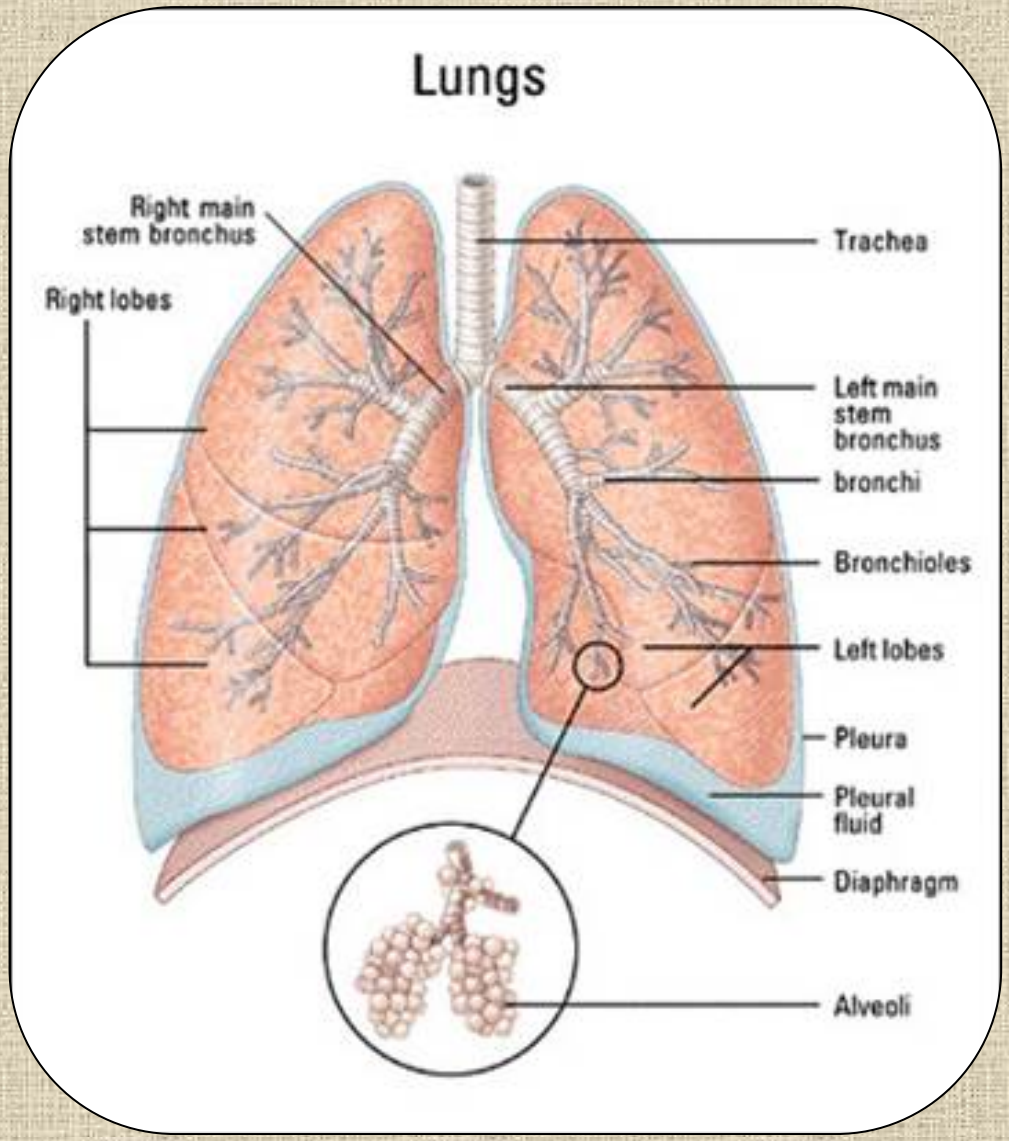
[1] Cisternas M, et al., A comprehensive study of the direct and indirect costs of an adult with asthma. *J Allergy Clin Immunol* 2003; 111(6): 1212-1218

Airway Anatomy

Upper Respiratory System

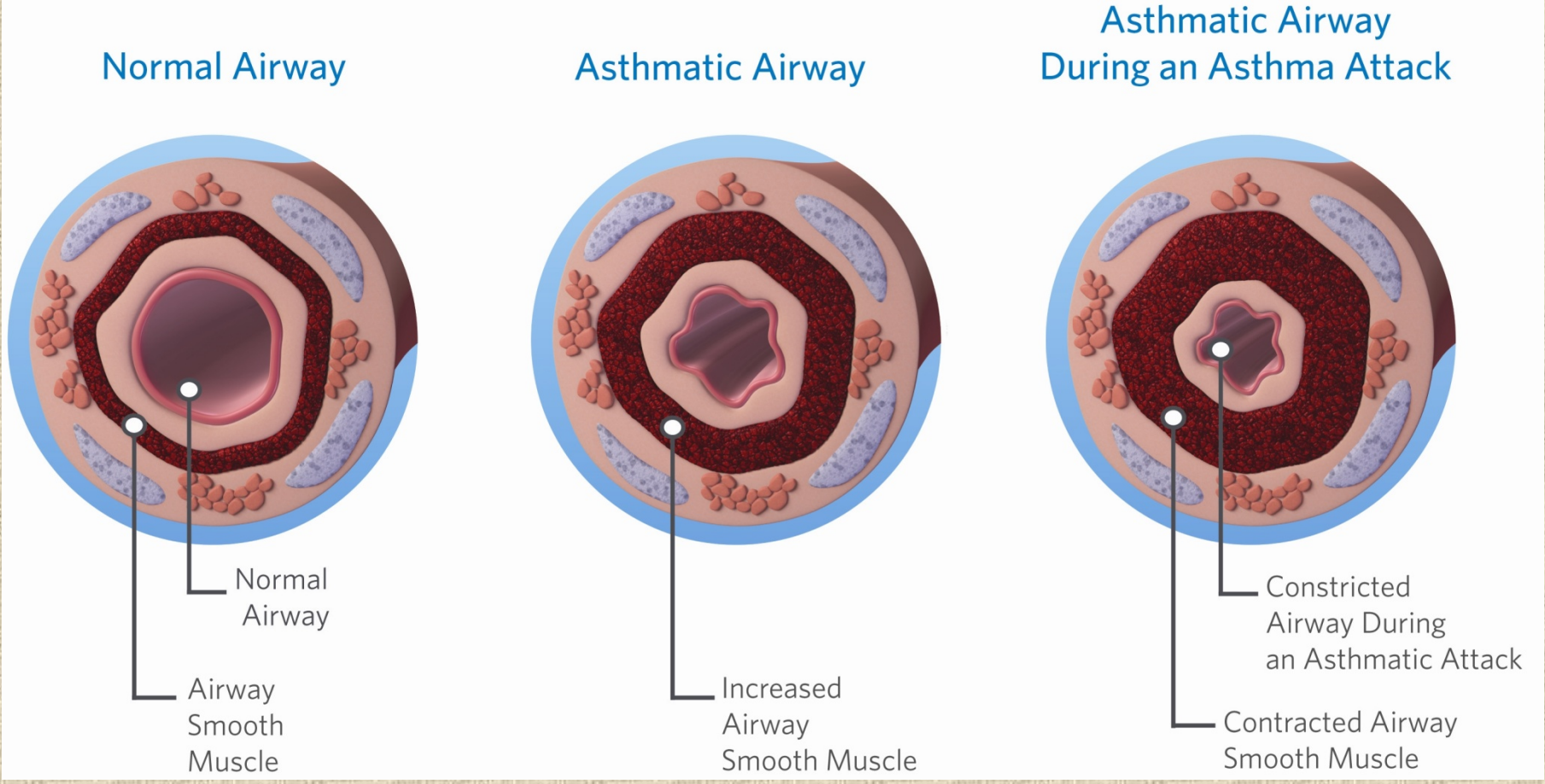


Lower Respiratory System

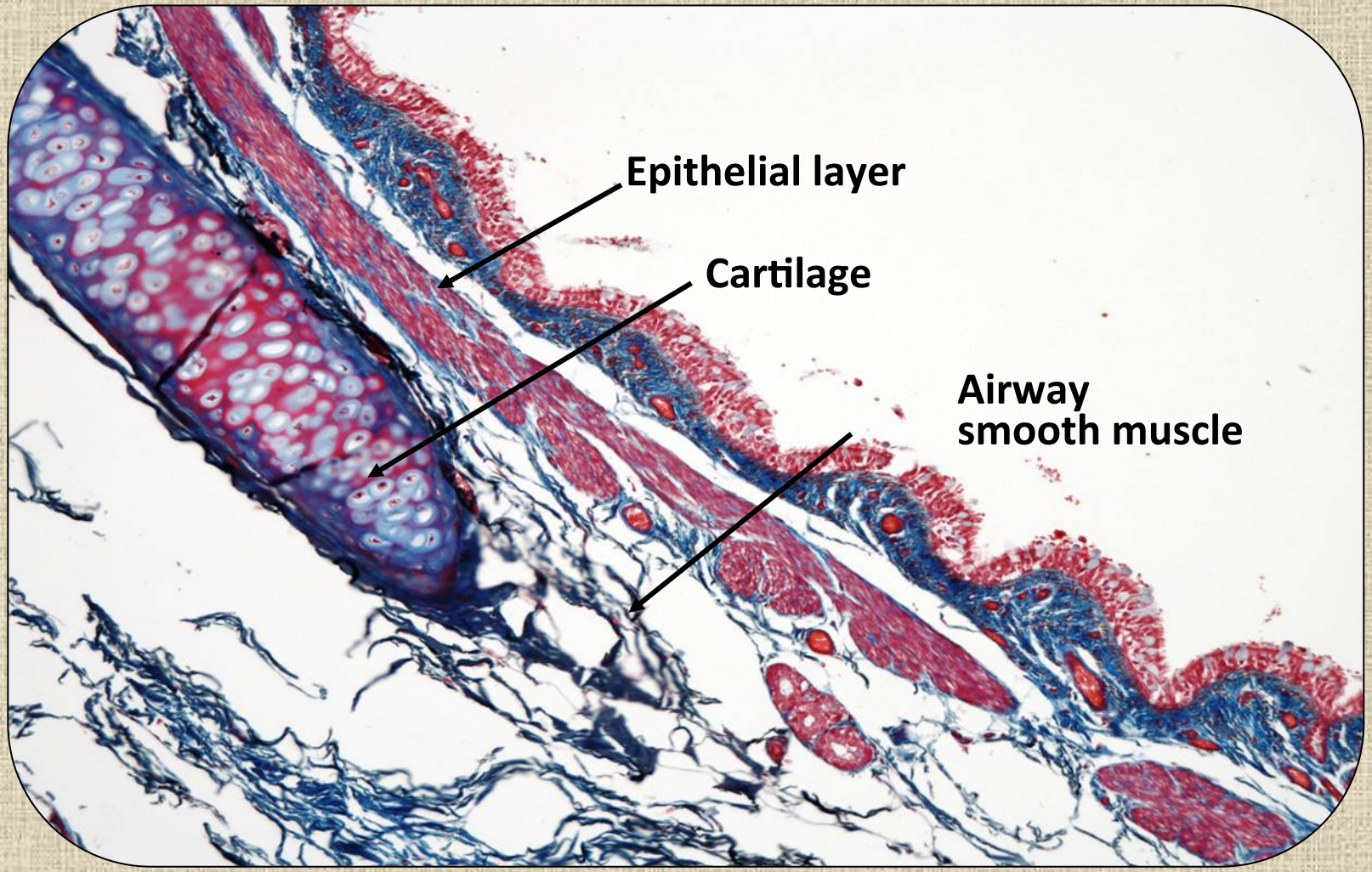


Airway Divisions

Role of Airway Smooth Muscle in Asthma



Airway Wall Histology



Medical Therapy

NAEEP Asthma Guidelines-Severity

FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

— **Assessing severity and initiating treatment for patients who are not currently taking long-term control medications**

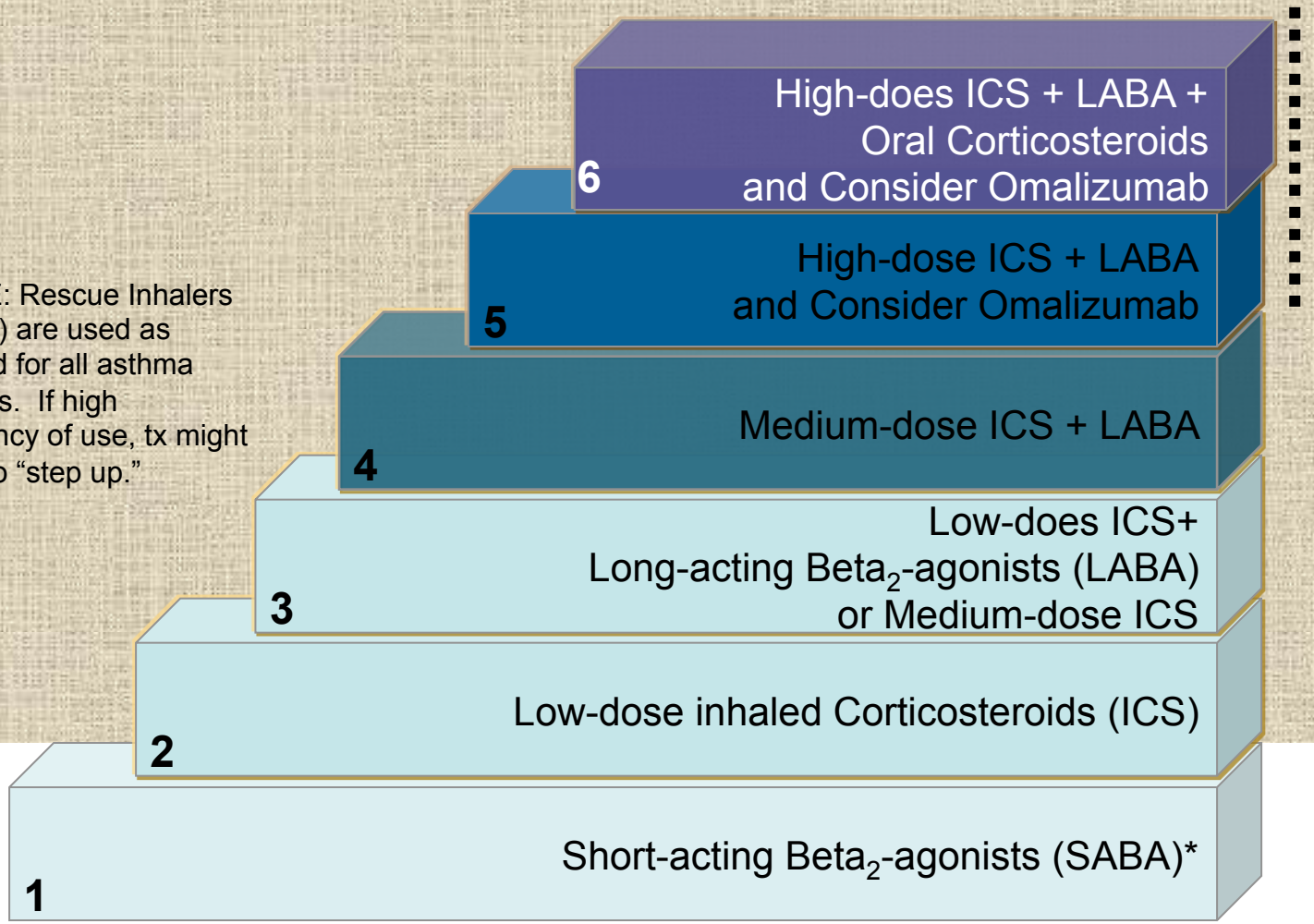
Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20 –39 yr 80% 40 –59 yr 75% 60 –80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal 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 systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment (See figure 4–5 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

NAEEP Asthma Guidelines-Control

FIGURE 4–7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (≥12 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires			
	ATAQ	0	1–2	3–4
	ACQ	≤0.75*	≥1.5	N/A
	ACT	≥20	16–19	≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (see figure 4–5 for treatment steps)		• Maintain current step. • Regular followups every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step and • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Stepwise Approach for Managing Asthma



Target Population For BT

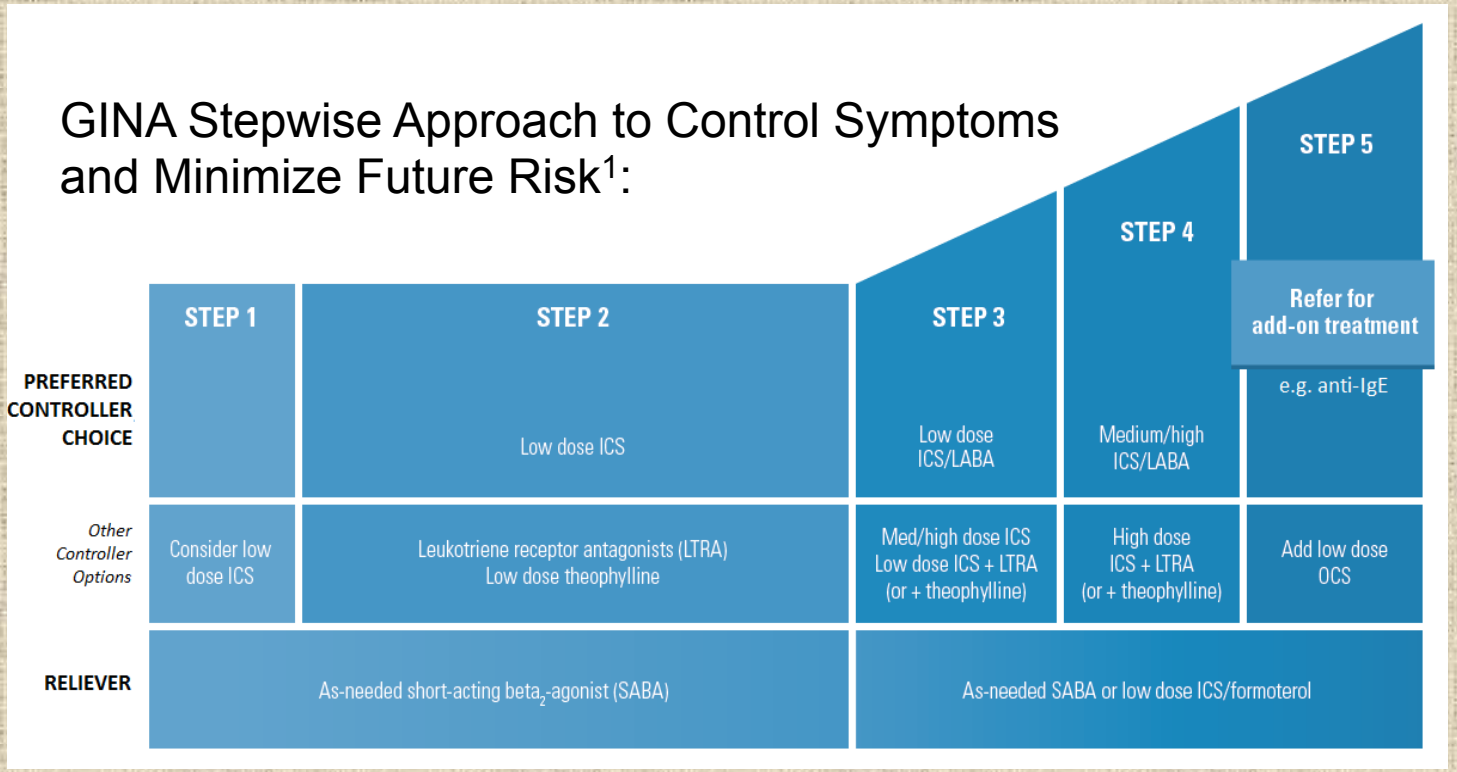
*NOTE: Rescue Inhalers (SABA) are used as needed for all asthma patients. If high frequency of use, tx might need to "step up."

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

Limited Medication Options Beyond ICS/ LABA for Severe Asthma

- **OCS (oral glucocorticosteroids)**
  - Effective for some, but associated with substantial long-term side effects
- **Anti-IgE therapy (omalizumab)**
  - Applicable only to patients with severe allergic asthma with elevated IgE levels
- **Other**
  - Theophylline – Limited efficacy in asthma and side effects are common
  - Tiotropium – Not approved for asthma; data show improved lung function and decreased reliever use
  - Leukotriene Receptor Antagonist (LTRA) - may be helpful for patients found to be aspirin sensitive

All this relates to BT how?



Bronchial Thermoplasty*

is included as a preferred add-on treatment option in Step 5

Chronic OCS is an option after other add-on treatments are considered

*Non-pharmacological add-on intervention

1. Adapted from Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, updated 2014. www.ginasthma.org/documents/4

BT Indication

FDA Indication: The Alair® Bronchial Thermoplasty System has been approved by the FDA for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta-agonists.

- Adult severe, persistent asthmatics (≥ 18 years old)
- Inadequate control despite combination of inhaled high dose corticosteroids (ICS) and a long-acting beta-agonists (LABA)
- Able to safely undergo bronchoscopy per hospital guidelines

Bronchial Thermoplasty:

Bronchial Thermoplasty

↓

Reduces Airway Smooth Muscle (ASM)

↓

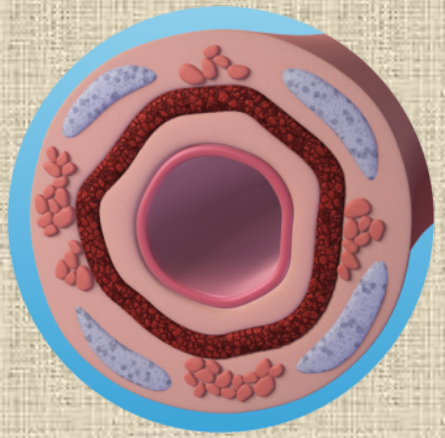
Reduces Bronchoconstriction

↓

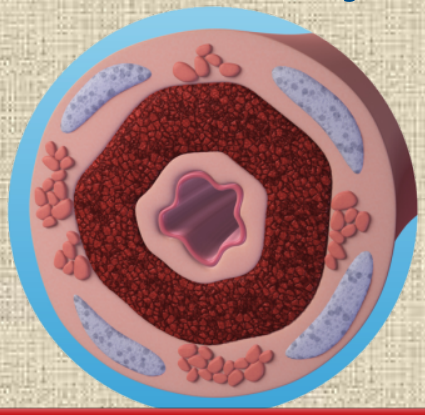
Reduces Asthma Exacerbations

↓

Improves Asthma Quality of Life



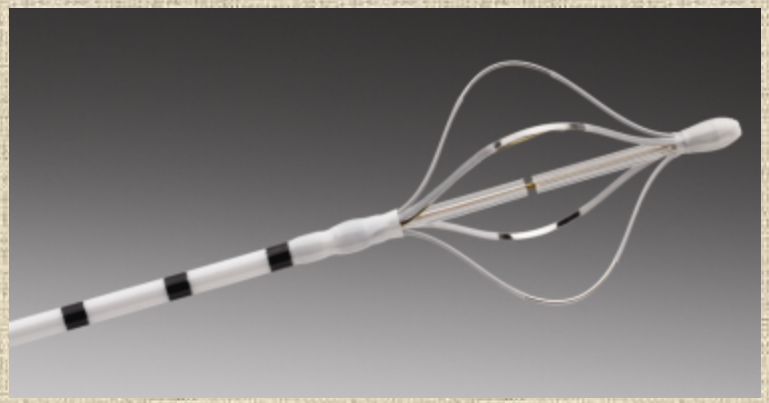
Normal Airway



Asthma Attack

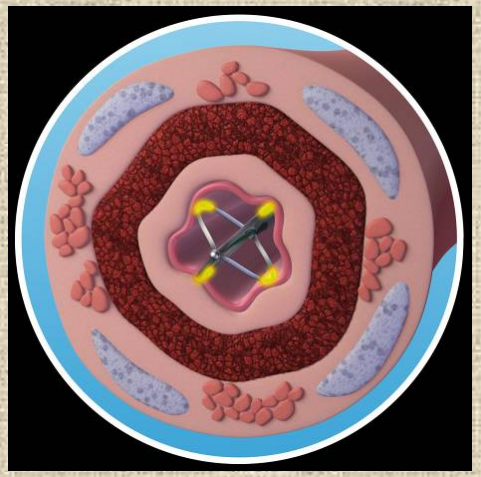
Bronchial Thermoplasty System

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



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

What is Bronchial Thermoplasty?

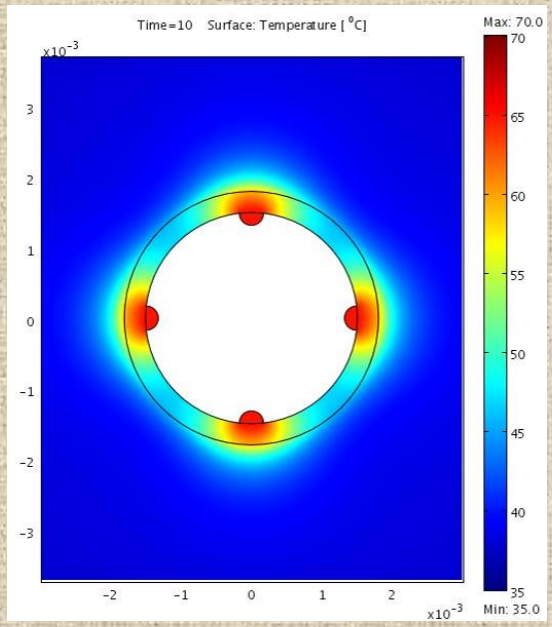


Outpatient procedure that delivers radiofrequency energy in a controlled fashion heating the airways to 65^0 C via a bronchoscope.

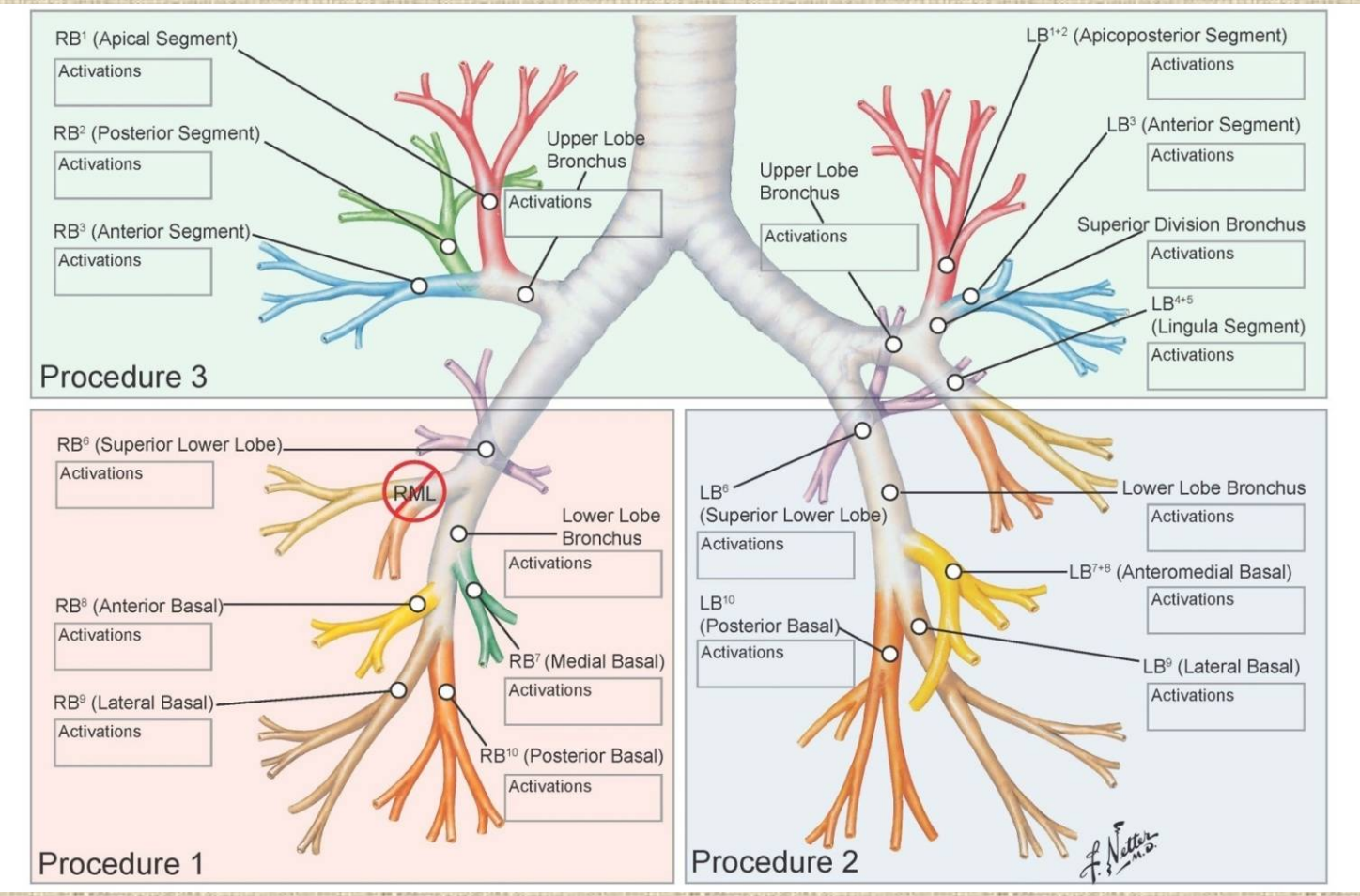
The procedure reduces excess airway smooth muscle by about 30-50%

Performed over 3 treatment sessions

- Treatment #1 right lower lobe
- Treatment #2 Left lower lobe
- Treatment #3 both upper lobes.



Three Treatment Sessions



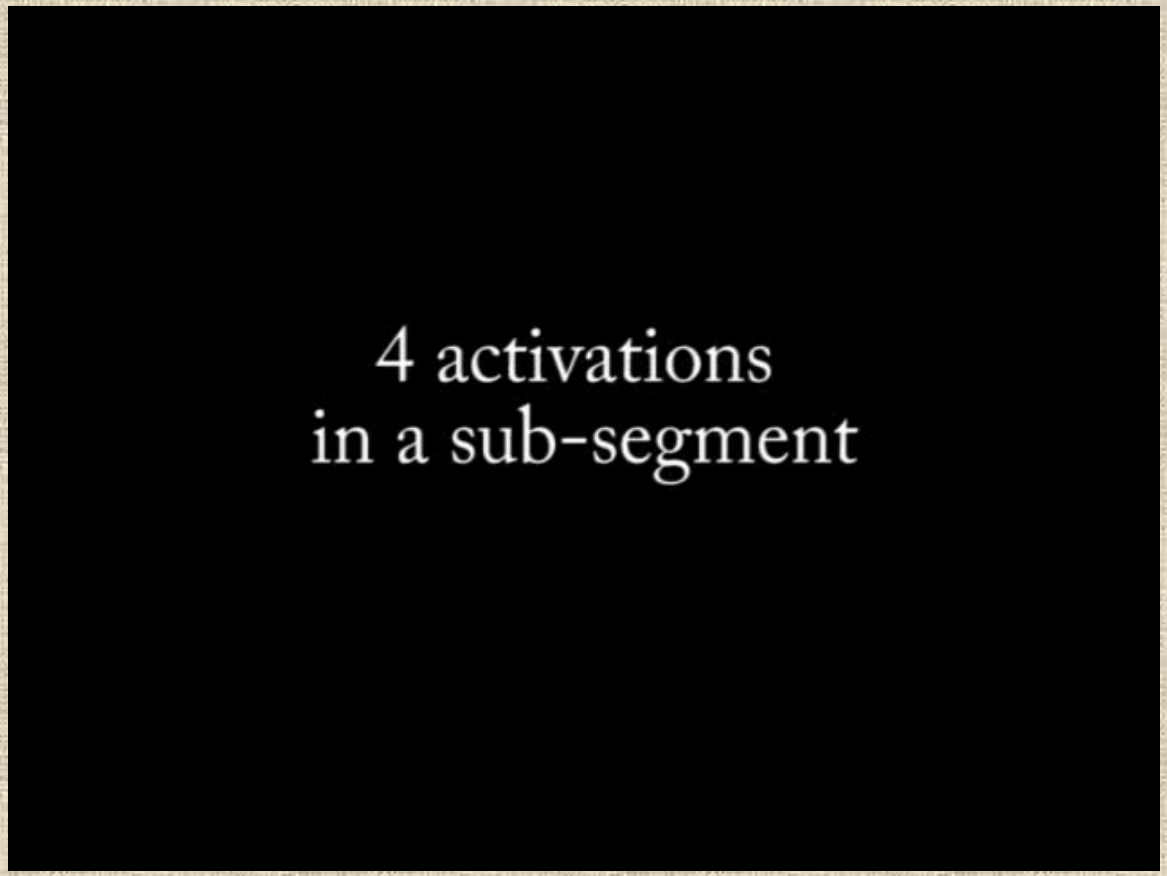
Bronchial Thermoplasty is performed in 3 separate treatment sessions each scheduled approximately 3 weeks apart

Bronchial Thermplasty Animation

Bronchial Thermoplasty i performed in 3 separate treatment sessions each scheduled approximately 3 weeks apart

Application of RF Energy

Temperature controlled energy (65^0 C) is delivered to airway wall for 10 seconds per activation – no permanent damage to epithelium



Application of RF Energy

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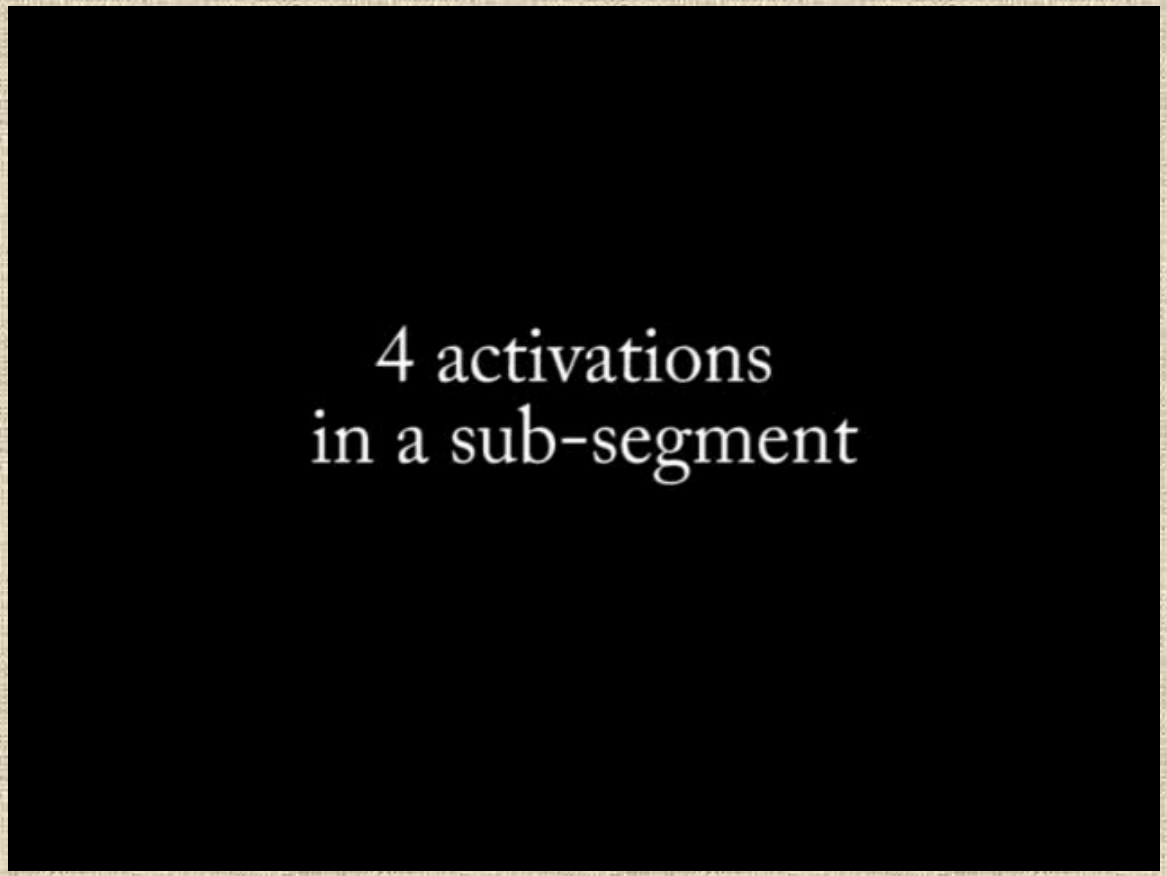
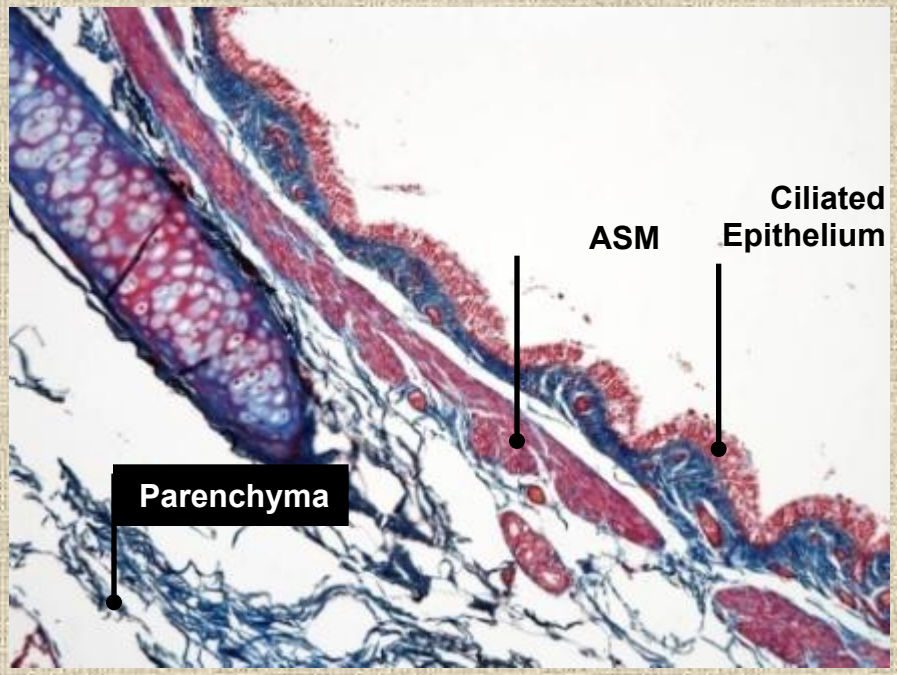
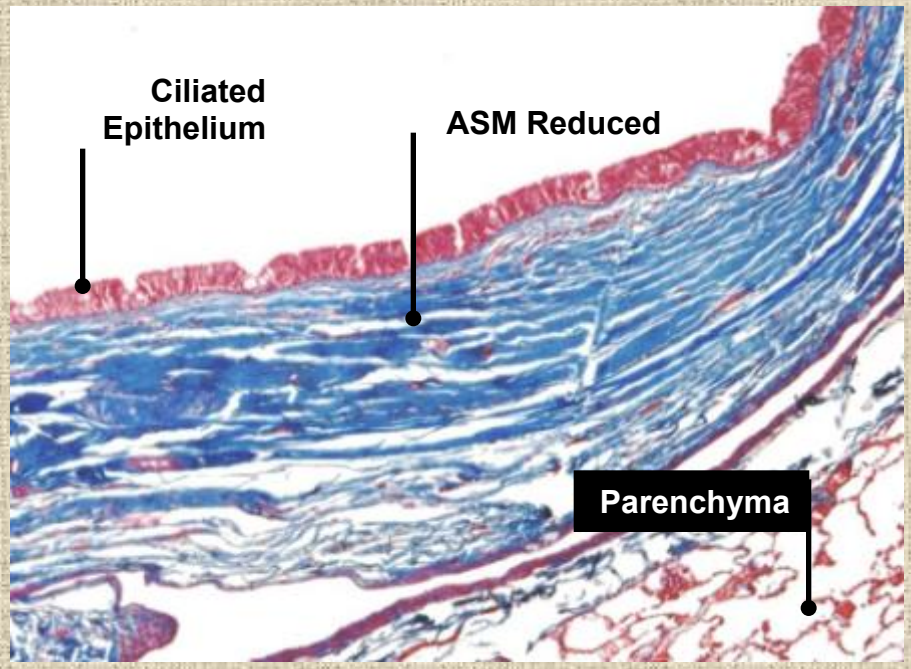


Reduced Airway Smooth Muscle

3 years post-treatment (canine model)

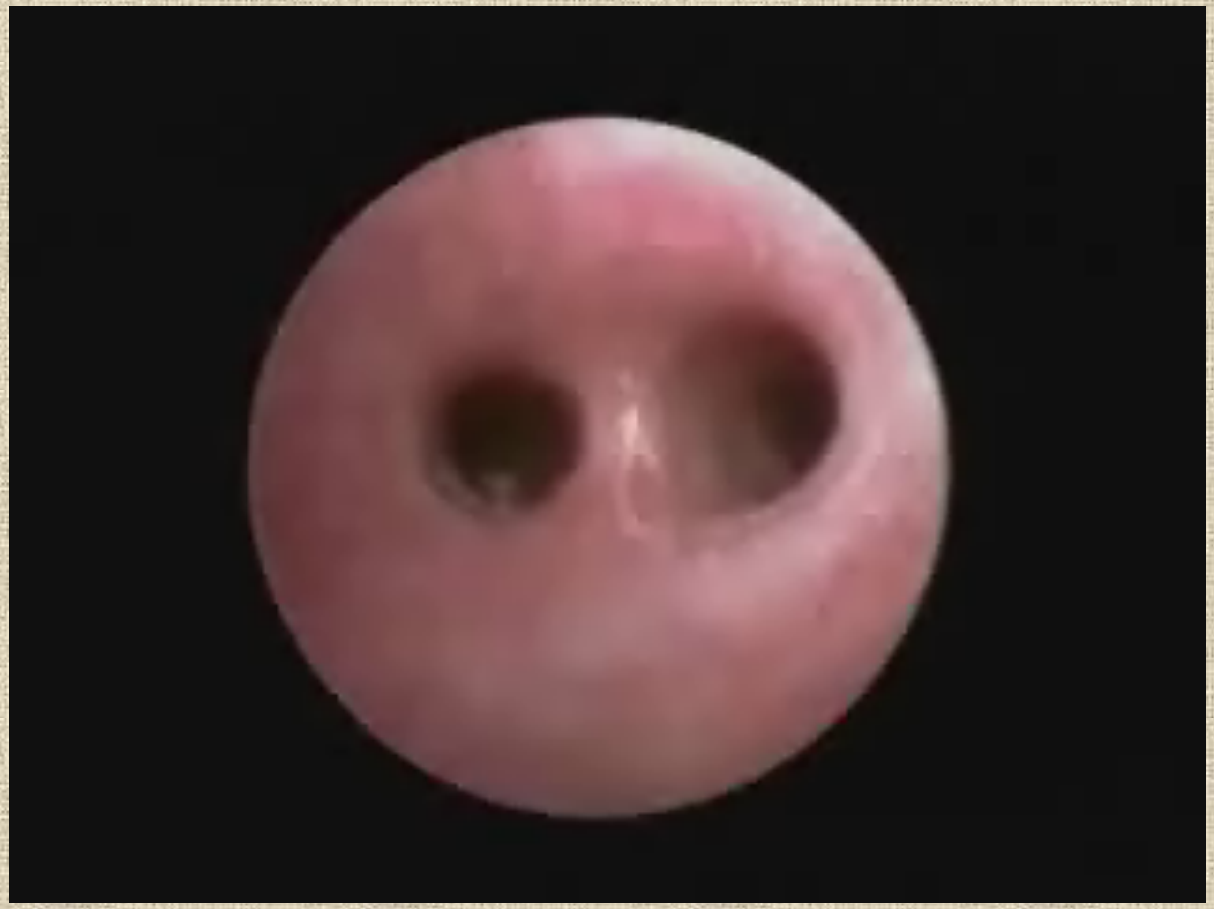




UNTREATED **TREATED**

Masson's Trichrome stain

Airway Responsiveness to Local Methacholine Challenge



Canine Model: Airway on left treated with bronchial thermoplasty. Airway on right was not treated.

Cox et al. Eur Respir Journal. 2004;24: 659-663

Bronchial Thermoplasty Studies

AIR2[1] 2005-2012	• Randomized, double-blind, sham-controlled study • N = 190 (190 BT, 98 sham) • Evaluate safety and effectiveness in patients with severe persistent asthma
RISA[2] 2004-2010	• Randomized, controlled study • N = 16 • Evaluate safety and reduction in medications and asthma symptoms in patients with severe, refractory asthma
AIR[3] 2002-2010	• Randomized, controlled study • N = 55 • Evaluate safety and reduction in patients with moderate to severe asthma
Feasibility[4] 2000-2007	• Non-randomized, prospective study • N = 16 • Evaluate safety in patients with mild to severe asthma

- **4 clinical studies** in patients with asthma
- **3 randomized, controlled,** clinical studies, with **1 sham-controlled**
- **5 years of follow-up**
- All BT studies published in top **peer-reviewed journals**

AIR2 = Asthma Intervention Research 2
RISA = Research in Severe Asthma
AIR = Asthma Intervention Research

1. Castro et al., AJRCCM 2010; Castro et al., AnnAAI 2011; Wechsler et al., JACI 2013
2. Pavord et al., AJRCCM 2007; Pavord et al., AnnAA 2013
3. Cox et al., NEJM 2007; Thomson et al., BMC Pulmonary Medicine 2011
4. Cox et al., AJRCCM 2006; Cox et al., AJRCCM 2010

AIR2 – Trial Design

Study Design: Sham Controlled, Double Blind

- 2 : 1 randomization; BT: Sham
- BT Group (ICS + LABA + BT)
- Sham Group (ICS + LABA + Sham)

Study Size:

- 297 subjects
- 30 centers in 6 countries (15 centers in the U.S.)

Length of Follow-up:

- One year (3, 6, 9 and 12 months)
- 5-year safety follow-up for BT subjects in Extension Study

BT = Bronchial Thermoplasty

AIR2 Trial – 1 year Key Findings

Key Findings at 1 Year after BT

Improved asthma-related quality of life compared to control (AQLQ score)

- 79% of BT-treated patients achieved ≥ 0.5 increase versus 64% of sham-treated patients (PPS 99.6%)

Improved clinical outcomes compared to Sham-control:

- 32% decrease in severe exacerbations
- 84% reduction in ER visits for respiratory symptoms
- 73% reduction in hospitalization for respiratory symptoms
- 66% less days lost from work, school and other daily activities due to asthma

No unanticipated device-related adverse events or deaths

Acceptable safety profile

PPS – posterior probability of superiority

Procedure Safety[1]

850 bronchoscopies performed in patients with severe asthma (558 BT and 292 Sham procedures)

No device-related deaths or major adverse events

- e.g., Pneumothorax, mechanical ventilation, airway stenosis or focal narrowing

More respiratory adverse events were reported in the BT group in the short-term after the procedure

- Typically occurring within one day and resolving within one week with standard care

Fewer respiratory adverse events, hospitalizations and ER visits in the BT group during post-treatment period[a]

a/ 6 weeks after the last bronchoscopy procedure to 12 month follow-up.

BT = Bronchial Thermoplasty

Risk of Respiratory-Related Hospitalization Following Procedure[1]

Respiratory-Related Hospitalizations during Treatment Period[a]	**BT** (N=190)	**Sham** (N=98)
Events / Subject (%)	19/190 (10%)*	2/98 (2.0%)
Events / Bronchoscopy (%)	19/558 (3.4%)	2/292 (0.7%)

* 10/19 (53%) in the BT group occurred on the day of the procedure.

a/ Time period beginning at first bronchoscopy to 6 weeks after the third bronchoscopy (approx. 12 week period)

BT = Bronchial Thermoplasty

Respiratory Symptoms Resulting in Hospitalization Following Procedure[1]

BT (N=190) 19 Hospitalizations in 16 Subjects No. of Events (Incident Rate %)		**Sham** (N=98) 2 Hospitalizations in 2 Subjects No. of Events (Incident Rate %)	
Asthma Aggravated	12 (6.3%)	Asthma Aggravated	2 (2.0%)
Atelectasis	3 (1.6%)		
Lower Resp. Tract Infection	1 (0.5%)		
Hemoptysis	1 (0.5%)		
Low FEV_1	1 (0.5%)		
Aspirated Prosthetic Tooth in Airway	1 (0.5%)		

BT = Bronchial Thermoplasty

AIR2 Extension Study: 5-Year Trial

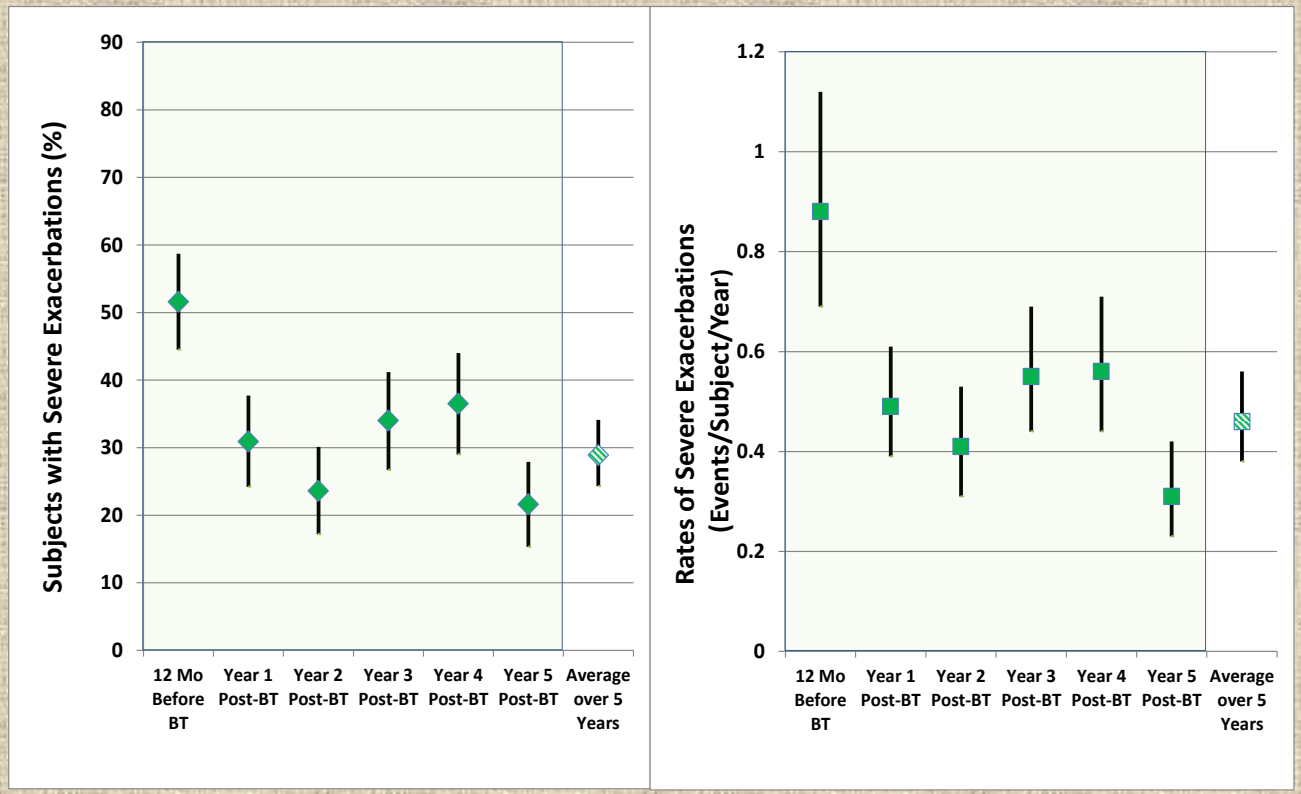
Period of Follow-up	Number of BT Subjects
12 Months	181
2 Years	165
3 Years	162
4 Years	159*
5 Years	162

* 4 subjects missed visit but remained in Study

- Retention rate from original 190 subjects treated = 85.3%
- Retention rate from subjects entering long-term follow-up = 89.5%

1. Wechsler, ATS 2013 [Poster Board # 308] Benefits Of Bronchial Thermoplasty Persist Out To 5 Years In Patients With Severe Asthma, [Publication Page: A3868]

Persistence of Effect at Five Years[1]
Exacerbations



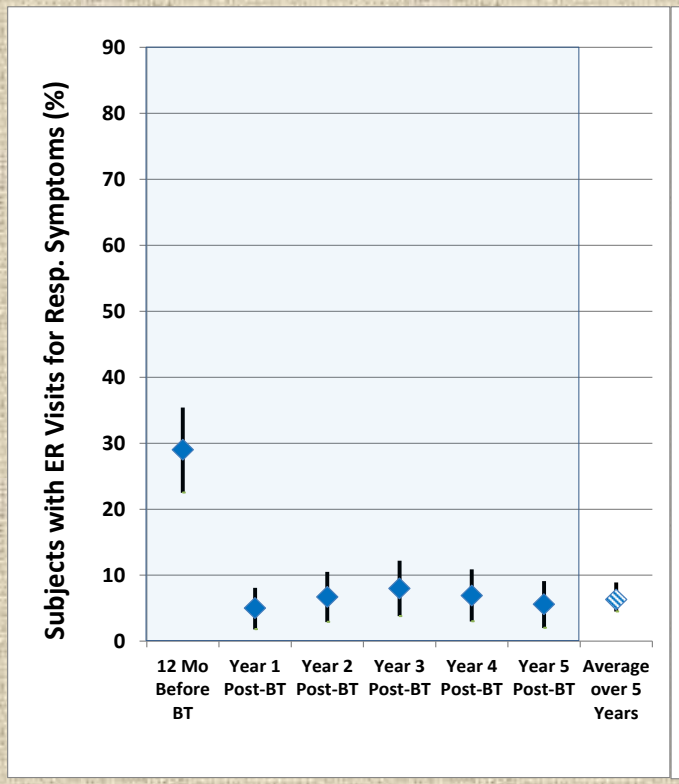
Non-inferiority margin met for Years 2-5 versus Year 1

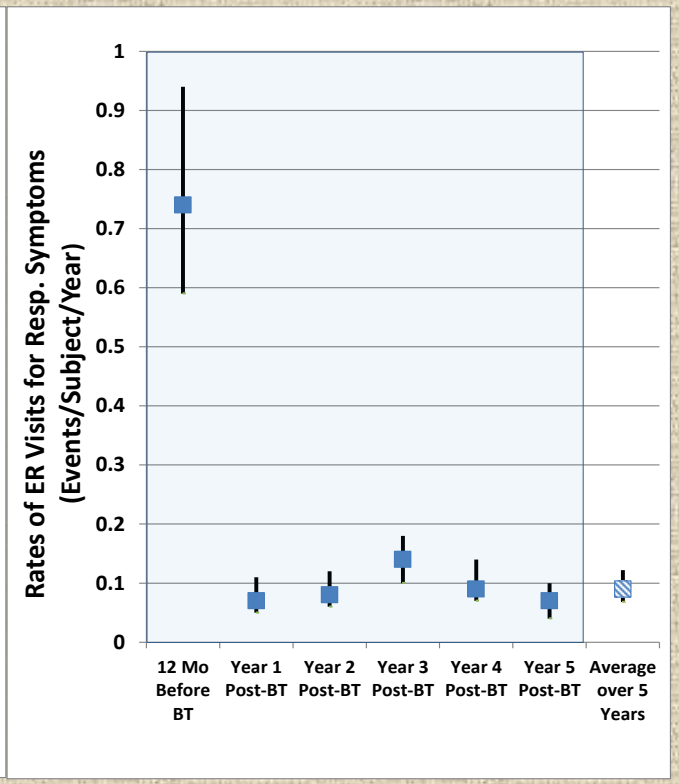
Compared to the 12 months prior to BT treatment:

- 44% average decrease in proportion of subjects having severe exacerbations
- 48% average decrease in severe exacerbation event rates

1. Wechsler, ATS 2013 [Poster Board # 308] Benefits Of Bronchial Thermoplasty Persist Out To 5 Years In Patients With Severe Asthma, [Publication Page: A3868]

Persistence of Effect at Five Years[1]
ER Visits for Respiratory Symptoms





Compared to the 12 months prior to BT treatment:

- 78% average decrease in Subjects having ER visits
- 88% average decrease in ER visit event rates

1. Wechsler, ATS 2013 [Poster Board # 308] Benefits Of Bronchial Thermoplasty Persist Out To 5 Years In Patients With Severe Asthma, [Publication Page: A3868]

AIR2 5-Year Extension Safety

Over 5 years following BT :

No increase in respiratory adverse events

No increase in asthma (multiple symptoms) adverse events

No increase in respiratory hospitalizations

No change in pre-bronchodilator FEV_1

No structural changes of a safety concern in high resolution CT scan – Baseline vs. 5 Year

- No evidence of an increase in bronchiectasis (localized, irreversible dilatation of part of the bronchial tree caused by destruction of the muscle and elastic tissue).

No respiratory-related deaths

Summary

Asthma is a relatively common disease characterized by bronchocontriction usually mediated by inflammation.

Most asthma responds well to medical therapy, however a small subgroup of patients will continue to experience frequent symptoms and exacerbations in spite of maximal medical therapy.

Bronchial Thermoplasty has been demonstrated to reduced frequency of exacerbations, hospitalizations and ED visits in patients with severe persistant asthma.

Who is Appropriate for Bronchial Thermoplasty?

FDA Indication: The Bronchial Thermoplasty System has been approved by the FDA for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta-agonists.

Adult severe, persistent asthmatics (≥ 18 years old)

Inadequate control despite combination of inhaled high dose corticosteroids (ICS) and a long-acting beta-agonists (LABA)

Able to safely undergo bronchoscopy per hospital guidelines

Contraindications

BT should not be performed on:

- Patients that have a pacemaker, internal defibrillator, or other implantable electronic device
- Patients that have a known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines
- Patients that have previously been treated with Bronchial Thermoplasty.

Contraindications

BT should be delayed for the following:

- Active respiratory infection
- Asthma attack or changing dose of systemic corticosteroids (up or down) in the past 14 days
- Known bleeding disorder
- Patient is unable to stop taking anticoagulants, antiplatelet agents, aspirin or non-steroidal anti-inflammatory medications (NSAIDS) before the procedure with physician guidance

Precautions

Patients with these conditions were not studied in the AIR2 pivotal trial and the safety of BT System treatment for such patients has not been determined.

- Post-bronchodilator FEV_1 < 65%
- Other respiratory diseases including emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis, or uncontrolled obstructive sleep apnea
- Use of short acting bronchodilator ≥12 puffs per day within 48 hours of bronchoscopy (excluding prophylactic use for exercise)
- Use of oral corticosteroids ≥10 mg/day for asthma
- Increased risk for adverse events associated with bronchoscopy or anesthesia, such as pregnancy, insulin dependent diabetes, epilepsy, or other significant co-morbidities, such as uncontrolled coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension
- Intubation for asthma, or ICU admission for asthma within the prior 24 months
- Any of the following within the past 12 months:
    i. 4 or more lower respiratory tract infections (LRTI)
    ii. 3 or more hospitalizations for respiratory symptoms
    iii. 4 or more OCS pulses for asthma exacerbation