Bronchial Thermoplasty
A Revolutionary Treatment for the Severe Asthmatic

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IMPACT

• Affects 300 million people worldwide
• Projected to increase by 100 million in next 15-20 years (mainly kids) Increased western lifestyles and urbanization
• Accounts for 1 out of every 250 deaths
• Profound health-care costs in terms of emergency and hospitalizations
• Indirect costs with missed work and school absenteeism
• Disability-adjusted life years comparable to DM, liver cirrhosis and schizophrenia (15 million/yr or 1% of all DALY’s worldwide)
• 50% of total health care costs from those that fail to respond to conventional therapy

Asthma Facts

• Nearly 25M people suffer from asthma in the U.S.

• Every day in the U.S.:
  – 44,000 people have an asthma attack
  – 27,000 adults miss work due to asthma
  – 4,700 people visit the emergency room due to asthma
  – 1,200 people are admitted to the hospital due to asthma
  – 9 people die from asthma

• The annual cost of asthma is estimated to be nearly $18 billion – due to medications, healthcare costs and lost productivity

Asthma and Allergy Foundation of America: [http://www.aafa.org/print.cfm?id=8&sub=42](http://www.aafa.org/print.cfm?id=8&sub=42) (Accessed March 2013)
Disparities in Asthma

- **Current asthma prevalence is higher among:**
  - Children than adults
  - Boys than girls
  - Women than men
  - African Americans than Caucasians

- **African Americans have higher morbidity and mortality rates:**
  - 3 times more likely to be hospitalized from asthma
  - 2.5 times more likely to die from asthma than Caucasian women

Asthma and Allergy Foundation of America: [http://www.aafa.org/print.cfm?id=8&sub=42](http://www.aafa.org/print.cfm?id=8&sub=42) (Accessed March 2013)
Higher Cost of Severe Asthma (U.S.)

Higher healthcare costs with asthma severity\(^2\)

$2,200

$4,800

$12,800

\begin{itemize}
  \item Increased healthcare utilization
  \item Emergency Room (ER) visits and Hospitalizations
  \item Patients with exacerbations have higher health care costs than patients without exacerbations\(^3\)
\end{itemize}

Control of Asthma

- **Reduce Impairment**
  - Prevent troublesome symptoms
  - Decrease use of inhaled SABA for quick relief
  - Maintain normal pulmonary function
  - Normal activity
  - Meet pt. and family expectations

- **Reduce Risk**
  - Prevent recurrent exacerbations and minimize ED/Hospital stays
  - Prevent loss of lung function
  - Provide optimal pharmacotherapy with minimal or no side effects
Barriers

- Generic barriers including poverty, poor education, and poor infrastructure
- Environmental barriers including indoor and outdoor air pollution, tobacco smoking, and occupational exposures
- Low public health priority due to the importance of other respiratory illnesses such as tuberculosis and pneumonia and the lack of data on morbidity and mortality from asthma
- Unsustainable generalizations across cultures and health care systems which may make management guidelines developed in high-income countries difficult to implement in low and middle-income countries.
- Inherent barriers in the organization of health care services in terms of
  - geography
  - type of professional responding
  - education and training systems
  - public and private care
  - tendency of care to be "acute" rather than "routine"

Barriers

- The limited availability and use of medications including
  - omission of basic medications from WHO or national essential drug lists
  - poor supply and distribution infrastructure
  - cost
  - cultural attitudes towards drug delivery systems, e.g. inhalers
- Patient barriers including
  - cultural factors
  - lack of information
  - underuse of self-management
  - over-reliance on acute care
  - use of alternative unproven therapies
- Inadequate government resources provided for health care including asthma

The presence of widespread narrowing of the airways which alters in severity either spontaneously or as a result of treatment.
Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.
GREEK ANTIQUITY

• Aretaeus of Cappadocia
• Lived 500 years after Hippocrates
• Master clinician
• Best clinical description of asthma in antiquity

Asthmatic prodromal symptoms:

... Heaviness of the chest; sluggishness to one`s accustomed work and to every other exertion; difficulty when running or on a steep road; they are scarce and troubled with cough; flatulence and extraordinary movements in the hypochondrium; restless; heat at night small and imperceptible; nose sharp and ready for respiration.

Asthmatic attack:

... The face is red, the eyes protruberant, as if from much worse in sleep; voice is liquid and without resonant. These symptoms lead them to take cold air, they eagerly go into the open air, in fear of the absence of air; they breathe standing, and in their want of air, they also open the mouth as if best to enjoy the more of it; sweat about the forehead and clavicles; cough incessant and laborious; expectoration small, thin, resembling the efflorescence of foam; neck swells, pulse small, dense, compressed, legs slender.

Asthma Pathogenesis

- Airways infiltrated with eosinophils and mononuclear cells
- Vasodilation and microvascular leakage
- Airway smooth muscle hypertrophy
- New vessel formation
- Increased numbers of epithelial goblet cells
- Deposition of interstitial collagens beneath the epithelium
Airway smooth muscle constriction during an asthma attack

Normal Airway

Asthma Attack

Ref: ENDO-15402-AB
Asthma Treatment

Severe Asthma

- Diagnosis confirmed and comorbidities addressed
- Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS# and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥ 50% of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy.


Uncontrolled Asthma

• Evidence of any one of criteria while on high-dose therapy:

  1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or “not well controlled” by NAEPP/GINA guidelines)

  2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year

  3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

  4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

• Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

• Future risk and medication side effects

Natural History of Severe Asthma

- Knowledge is limited
- Prevalence estimated at about 5-10% of total asthma population
- Early or gradually over time
- Severe asthma phenotypes are associated with:
  - Genetic factors, age of onset, disease duration, exacerbations, sinus disease and inflammatory characteristics

Risk Factors for Severe Asthma

- Persistent eosinophilic inflammation
- Nasal polyps, sinusitis, ASA sensitivity
- Infections (Chlamydia)
- Occupational exposures
- Obesity
- Tobacco smoke and environmental air pollution
- Increased exacerbations linked to:
  - Severe sinus disease, GERD, recurrent respiratory infections, OSA
- Fungal sensitization (Aspergillus)

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Evaluation of the Severe Asthmatic

- Be a skeptic
- Misdiagnosis of non-asthmatic conditions as uncontrolled asthma 12-30%
- Careful history and physical
- Spirometry with reversible airflow limitation
- Referral to a specialized center resulted in 30-50% going from definition of severe to difficult-to-control


Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. *Am Rev Respir Dis* 1987; 136: 225–244.
<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunctional breathing/vocal cord dysfunction</td>
<td>Dysfunctional breathlessness/vocal cord dysfunction</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Recurrent aspiration, reflux, swallowing dysfunction</td>
<td>Hyperventilation with panic attacks</td>
</tr>
<tr>
<td>Prematurity and related lung disease</td>
<td>Bronchiolitis obliterans</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Congenital or acquired immune deficiency</td>
<td>Adverse drug reaction [e.g. angiotensin-converting enzyme inhibitors]</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>Bronchiectasis/cystic fibrosis</td>
</tr>
<tr>
<td>Central airways obstruction/compression</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Hyper eosinophilic syndromes</td>
</tr>
<tr>
<td>Congenital malformations including vascular ring</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>Tracheobronchomalacia</td>
<td>Herpetic tracheobronchitis</td>
</tr>
<tr>
<td>Carcinoid or other tumour</td>
<td>Endobronchial lesion/foreign body [e.g. amyloid, carcinoid, tracheal stricture]</td>
</tr>
<tr>
<td>Mediastinal mass/enlarged lymph node</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Acquired tracheobronchomalacia</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td></td>
</tr>
</tbody>
</table>
Assess Comorbidities

- Non-adherence to treatment (32-56%)
- Check with pharmacies
- Medication cost implications
- Poor technique with inhaler administration

<table>
<thead>
<tr>
<th>TABLE 7 Comorbidities and contributory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Rhinosinusitis (adults), nasal polyps</td>
</tr>
<tr>
<td>2) Psychological factors: personality trait, symptom perception, anxiety, depression</td>
</tr>
<tr>
<td>3) Vocal cord dysfunction</td>
</tr>
<tr>
<td>4) Obesity</td>
</tr>
<tr>
<td>5) Smoking/smoking related disease</td>
</tr>
<tr>
<td>6) Obstructive sleep apnoea</td>
</tr>
<tr>
<td>7) Hyperventilation syndrome</td>
</tr>
<tr>
<td>8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders</td>
</tr>
<tr>
<td>9) Gastro-oesophageal reflux disease (symptomatic)</td>
</tr>
<tr>
<td>10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, angiotensin-converting enzyme inhibitors</td>
</tr>
</tbody>
</table>


Component 2: Control of Factors Contributing to Asthma Severity

Exposure of asthma patients to irritants or allergens to which they are sensitive has been shown to increase asthma symptoms and precipitate asthma exacerbations.
Assess, then reduce...

<table>
<thead>
<tr>
<th>Inhalant Allergens</th>
<th>Workplace Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient have symptoms year round? (If yes, ask the following questions. If no, see next set of questions.)</td>
<td>Does the patient cough or wheeze during the week, but not on weekends when away from work?</td>
</tr>
<tr>
<td>Does the patient keep pets indoors? What type?</td>
<td>Do the patient’s eyes and nasal passages get irritated soon after arriving at work?</td>
</tr>
<tr>
<td>Does the patient have moisture or dampness in any room of his or her home (e.g., basement)? (Suggests house-dust mites, molds.)</td>
<td>Do coworkers have similar symptoms?</td>
</tr>
<tr>
<td>Does the patient have mold visible in any part of his or her home? (Suggests molds.)</td>
<td>What substances are used in the patient’s workplace? (Assess for sensitizers.)</td>
</tr>
<tr>
<td>Has the patient seen cockroaches in his or her home in the past month? (Suggests significant cockroach exposure.)</td>
<td></td>
</tr>
<tr>
<td>Assume exposure to house-dust mites unless patient lives in a semi-arid region. However, if a patient living in a semi-arid region uses a swamp cooler, exposure to house dust mites must still be assumed.</td>
<td></td>
</tr>
<tr>
<td>Do symptoms get worse at certain times of the year? (If yes, ask when symptoms occur.)</td>
<td><strong>Rhinitis</strong></td>
</tr>
<tr>
<td>Early spring? (trees)</td>
<td>Does the patient have constant or seasonal nasal congestion and/or postnasal drip?</td>
</tr>
<tr>
<td>Late spring? (grass)</td>
<td></td>
</tr>
<tr>
<td>Late summer to autumn? (weeds)</td>
<td><strong>Gastroesophageal Reflux</strong></td>
</tr>
<tr>
<td>Summer and fall? (Alternaria, Cladosporium)</td>
<td>Does the patient have heartburn?</td>
</tr>
<tr>
<td></td>
<td>Does food sometimes come up into the patient’s throat?</td>
</tr>
<tr>
<td>Tobacco Smoke</td>
<td>Has the patient had coughing, wheezing, or shortness of breath at night in the past 4 weeks?</td>
</tr>
<tr>
<td>Does the patient smoke?</td>
<td>Does the infant vomit followed by coughing or have wheezy cough at night? Are symptoms worse after feeding?</td>
</tr>
<tr>
<td>Does anyone smoke at home or work?</td>
<td><strong>Sulfite Sensitivity</strong></td>
</tr>
<tr>
<td>Does anyone smoke at the child’s day care?</td>
<td>Does the patient have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?</td>
</tr>
<tr>
<td>Indoor/Outdoor Pollutants and Irritants</td>
<td><strong>Medication Sensitivities and Contraindications</strong></td>
</tr>
<tr>
<td>Is a wood-burning stove or fireplace used in the patient’s home?</td>
<td>What medications does the patient use now (prescription and nonprescription)?</td>
</tr>
<tr>
<td>Are there unvented stoves or heaters in the patient’s home?</td>
<td>Does the patient use eyedrops? What type?</td>
</tr>
<tr>
<td>Does the patient have contact with other smells or fumes from perfumes, cleaning agents, or sprays?</td>
<td>Does the patient use any medications that contain beta-blockers?</td>
</tr>
<tr>
<td></td>
<td>Does the patient ever take aspirin or other non-steroidal anti-inflammatory drugs?</td>
</tr>
<tr>
<td></td>
<td>Has the patient ever had symptoms of asthma after taking any of these medications?</td>
</tr>
</tbody>
</table>

1 These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.
**Figure 3-20. Summary of Measures to Control Environmental Factors That Can Make Asthma Worse**

**Allergens**

Reduce or eliminate exposure to the allergen(s) the patient is sensitive to, including:

- **Animal dander:** Remove animal from house or, at a minimum, keep animal out of the patient’s bedroom.
- **House-dust mites:**
  - **Recommended:** Encase mattress in an allergen-impermeable cover; encase pillow in an allergen-impermeable cover or wash it weekly; wash sheets and blankets on the patient’s bed in hot water weekly (water temperature of >150 °F is necessary for killing mites); cooler water and detergent and bleach will still reduce five and allergen level. Prolonged exposure to dry heat or freezing can also kill mites but does not remove allergen.
  - **Desirable:** Reduce indoor humidity to or below 50 percent, ideally 30–50 percent; remove carpets from the bedroom; avoid sleeping or lying on upholstered furniture; remove carpets that are laid on concrete.
- **Cockroaches:** Use poison bait or traps to control insects, but intensive cleaning is necessary to reduce reservoirs. Do not leave food or garbage exposed.
- **Pollens (from trees, grass, or weeds) and outdoor molds:** If possible, adults who have allergies should stay indoors, with windows closed, during periods of peak pollen exposure, which are usually during the midday and afternoon.
- **Indoor mold:** Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to or below 50 percent, ideally 30–50 percent. Dehumidify basements if possible.
- **Tobacco Smoke**

Advising patients and others in the home who smoke to stop smoking or to smoke outside the home. Discuss ways to reduce exposure to other sources of tobacco smoke, such as from daycare providers and the workplace.

**Indoor/Outdoor Pollutants and Irritants**

Discuss ways to reduce exposures to the following:

- Wood-burning stoves or fireplaces
- Unvented gas stoves or heaters
- Other irritants (e.g., perfumes, cleaning agents, sprays)
- Volatile organic compounds (VOCs) such as new carpeting, particle board, painting

Multifaceted approach is required; single steps to reduce exposure are generally ineffective.
Scotland 2006 Ban on smoking in public places
• Children < 15 years of age
• 2000 to 2009 hospital admissions for asthma
• Prior to legislation asthma admissions were increasing at a mean of 5.2% per year.
• After implementation mean reduction in rate of admissions of 18.2% per year relative to rate on March of 2006 (P<0.001)
• Subsequent reduction in rate of respiratory disease in populations other than those with occupational exposure to tobacco smoke
• Toronto (minus restaurants) and Arizona studies included adults

The Expert Panel concludes that ICSs are the most potent and consistently effective long-term control medication for asthma (Evidence A).

- Reduce symptoms
- Improve control and QOL
- Improve PEF and spirometry
- Decrease ED, hospital, acute care visits
- Reduce systemic steroid need
<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Threshold daily dose in μg considered as high</th>
<th>Age 6–12 years</th>
<th>Age &gt;12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>QVAR</td>
<td>≥800 (DPI or CFC MDI)</td>
<td>≥2000 (DPI or CFC MDI)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort/Symbicort</td>
<td>≥320 (HFA MDI)</td>
<td>≥1000 (HFA MDI)</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td></td>
<td>≥800 (MDI or DPI)</td>
<td>≥1600 (MDI or DPI)</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flovent/Advair</td>
<td>≥160 (HFA MDI)</td>
<td>≥320 (HFA MDI)</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Asmanex/Dulera</td>
<td>≥500 (HFA MDI or DPI)</td>
<td>≥1000 (HFA MDI or DPI)</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td></td>
<td>≥500 (DPI)</td>
<td>≥800 (DPI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1200</td>
<td>≥2000</td>
</tr>
</tbody>
</table>

Notes: 1) Designation of high doses is provided from manufacturers’ recommendations where possible. 2) As chlorofluorocarbon (CFC) preparations are being taken from the market, medication inserts for hydrofluoroalkane (HFA) preparations should be carefully reviewed by the clinician for the equivalent correct dosage. DPI: dry powder inhaler; MDI: metered-dose inhaler.
Steroid Side Effects

• OCS’s:
  – Increased risk of fracture and cataracts
  – Growth retardation and adrenal suppression in children
  – Obesity in adults

• ICS’s:
  – Adrenal suppression in children
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
Intervention Available When Medications Are Not Enough

GINA Stepwise Approach to Control Symptoms and Minimize Future Risk¹:

<table>
<thead>
<tr>
<th>PREFERRED CONTROLLER CHOICE</th>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
<th>STEP 5</th>
<th>Refer for add-on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Controller Options</strong></td>
<td>Consider low dose ICS</td>
<td>Leukotriene receptor antagonists (LTRA) Low dose theophylline</td>
<td>Med/high dose ICS Low dose ICS + LTRA (or + theophylline)</td>
<td>High dose ICS + LTRA (or + theophylline)</td>
<td>Add low dose OCS</td>
<td>e.g. anti-IL5</td>
</tr>
<tr>
<td><strong>RELIEVER</strong></td>
<td>As-needed short acting beta₂ agonist (SABA)</td>
<td>As-needed SABA or low dose ICS/formoterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Non-pharmacological add-on intervention


**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
BT Reduces Excess Airway Smooth Muscle (ASM)

Bronchial thermoplasty

Actual Procedure
Reduced Airway Smooth Muscle

- 3 years post-treatment (canine model)\(^1\)

Masson’s Trichrome stain
BT Treatment Effect – Airway Responsiveness to Local Methacholine Challenge \(^1\)

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

Asthma Intervention Research 2 (AIR2) Trial

Objective:
BT superior to sham

Primary Endpoint:
AQLQ score
(Asthma Quality of Life Questionnaire)

Other Endpoints and Analyses:
Severe exacerbations*, ER visits, Days lost from work/school/other daily activities due to asthma symptoms

† Study Population: patients with severe persistent asthma symptomatic despite high dose ICS (>1,000 µg/d beclomethasone or equivalent) + LABA (>100 µg/d salmeterol or equivalent).

2. Severe asthma classification based on treatment in Steps 5 or 6 per the NAEPP 2007 guidelines.
Demonstrated Clinical Effectiveness at 1 Year

- **Improved asthma-related quality of life compared to sham-control (AQLQ score)**
  - Difference in AQLQ score between groups was 0.21 (PPS=96.0%)
  - 1.35 mean improvement in BT group compared to Baseline
  - 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 (PPS=95.5%)
  - 84% reduction in emergency room (ER) visits for respiratory symptoms (PPS=99.9%)
  - 66% less days lost from work, school and other daily activities due to asthma (PPS=99.3%)

PPS = Posterior Probability of Superiority

## AIR2 Respiratory Adverse Events\(^1\)
Selected AEs with >3% incidence and difference between groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Period (~12 weeks)</th>
<th>Post-Treatment Period (~46 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BT (N=190)</td>
<td>Sham (N=98)</td>
</tr>
<tr>
<td>Asthma (Multiple Symptom)</td>
<td>52.1 %</td>
<td>38.8 *</td>
</tr>
<tr>
<td>Wheezing</td>
<td>15.3 %</td>
<td>6.1 *</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>4.7 %</td>
<td>0 *</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3.2 %</td>
<td>0 *</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>7.9 %</td>
<td>2.0 *</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>20.0 %</td>
<td>11.2 *</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.7 %</td>
<td>7.1</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>4.7*</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*Posterior Probability of Superiority (PPS) >95.0%

Demonstrated Clinical Safety at 1 Year

- No unanticipated device-related adverse events or deaths
  - e.g., Pneumothorax, airway stenosis or focal narrowing
- More respiratory adverse events were reported in the BT group in the short-term after the procedure
  - Most common respiratory AEs: asthma (multiple symptoms), upper respiratory tract infection, wheezing, chest pain, cough, and dyspnea
  - Typically occurring within one day and resolving within one week with standard care
  - Hospitalization rate for respiratory symptoms per bronchoscopy of 3.4%
- Fewer respiratory adverse events, hospitalizations and ER visits in the BT group in the long term
  (6 weeks after BT treatment to 12-month follow-up)

Note: 850 bronchoscopies were performed in patients with severe asthma
(558 BT and 292 sham procedures)

High Patient Satisfaction with BT

- **97%** of BT patients would “probably” or “definitely” recommend BT to a friend or family member.¹

AIR2 Trial
5-Year Extension Study
AIR2 Trial 5-Year Extension Study
Post Approval Study
AIR2 Extension Study

**Objective:**
Durability of effect

**Primary Endpoint:**
% of patients with severe exacerbation* at Years 2, 3, 4 and 5 is non-inferior to Year 1

**Secondary Endpoints:**
Severe exacerbations, ER visits for respiratory symptoms, Lung function (Pre-BD FEV₁), Respiratory adverse events


* Exacerbations requiring treatment with systemic corticosteroids or a doubling of ICS

Retention rate (from n=190) = 85.2%

1. **Randomized 2:1 (n=297)**
   - Year 0 (n=190)
   - Year 1 (n=181)
   - Year 2 (n=165)
   - Year 3 (n=162)
   - Year 4 (n=159)
   - Year 5 (n=162)

2. **BT**
   - Year 0 (n=98)
   - Year 1 (n=97)

3. **Sham**
   - Exit study
AIR2 Extension Study
Primary Endpoint Achieved

Demonstrated durability of effect:\

- Compared with Year 1, the percentage of BT patients experiencing severe exacerbations at Years 2, 3, 4 and 5 met the established non-inferiority margin.

Reduction in Severe Exacerbations Maintained out to 5 years\(^1\)

- The reduction in severe exacerbations requiring systemic corticosteroids at Year 1 was maintained out to at least 5 years.

Compared with 1 year prior to BT treatment (baseline):
- **44%** average decrease in percentage of patients having severe exacerbations
- **48%** average decrease in severe exacerbation event rates

Reduction in ER Visits Maintained out to 5 years

- The reduction in ER visits for respiratory symptoms at Year 1 was maintained out to at least 5 years.

Compared with 1 year prior to BT treatment (baseline):
- 78% average decrease in percentage of patients having ER visits
- 88% average decrease in ER visit event rates

Long-Term Safety Maintained out to 5 Years\(^1\)

- No increase seen in hospitalizations, asthma symptoms, or respiratory adverse events over the course of 5 years

- No structural changes in airways that were clinically significant were due to BT at 5 years (based on HRCT review)
  - No evidence of increase in bronchiectasis
  - No evidence of bronchiolitis obliterans or pulmonary emphysema in any patient

- Percent predicted pre-BD FEV\(_1\) values remained unchanged over the 5 years after BT. Post-BD FEV\(_1\) remained higher at all times; Increase in percent predicted FEV\(_1\) at baseline of 8.2% and at 5 years of 5.9%

How to Assess a BT Patient

- Confirmed diagnosis of severe asthma
- Evidence of adherence to ICS and LABA
- Demonstration of asthma impairments and/or risks of future exacerbations
  - Examples may include:
    - Chronic oral corticosteroid use
    - Anti-IgE therapy candidate or non-responder
    - Two or more severe exacerbations in the prior year
    - Impaired quality of life (assessed by AIS-6, ACT, AQLQ)
- Higher level care or add-on treatment needed
- Exclusion of BT contraindications
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 the Alair™ System
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
BT is performed by a BT-certified pulmonologist in 3 outpatient visits, typically scheduled 3 weeks apart.
Procedure Overview

- Patient evaluated pre-procedure to verify stability and ability to undergo bronchoscopy

- Prophylactic OCS (50mg/day) administered for 5 days (3 days before, day of, and day after procedure)

- Routinely performed under moderate sedation

- RF energy delivered to airways between 3-10 mm diameter (~60 activations per procedure) and typically completed in less than an hour

- Patient monitored 2-4 hours post-op and discharged home same day
  - Lung function stable within 80% of pre-procedure post-BD FEV₁
Post-Procedure/Patient Follow Up

- Patient contacted via phone at 1, 2 and 7 days to assess post procedure status
- Office visit at 2 to 3 weeks to assess clinical stability and schedule subsequent BT procedures as appropriate
- After BT treatment, patient returns to primary asthma physician for ongoing asthma management
- Patient evaluated for step-down therapy to determine lowest level of medication necessary to maintain asthma control