Severe Persistent Asthma and Bronchial Thermoplasty

Christopher DiBello MD
Pulmonary and Critical Care Medicine
PCCC of Volusia
Outline

• Burden of Severe Asthma
• Treatment of Severe Persistent Asthma
• Bronchial Thermoplasty (BT) Delivered by the Alair System
• Long-Term Clinical Outcomes out to 5 Years
• Who are the Right Patients for BT?
• How BT is Performed
What is Asthma

- Heterogenous disease usually characterized by chronic airway inflammation
- Defined by the history of respiratory symptoms such as wheeze, cough, shortness of breath, and chest tightness.
- They vary over time and intensity
- All of these together with variable expiratory airflow limitation
What is Asthma

• The variations are often triggered by factors such as: allergy or irritant exposure, exercise, viral illness, or change in weather.
• Symptoms and airflow limitation can resolve spontaneously, or with medications, and may sometimes be absent for weeks and months at a time.
• Some patients experience flare-ups or exacerbations which may be life threatening and have significant burden to patients and the community.
What is Asthma

- Asthma is a condition usually associated with airway hyperresponsiveness to direct and indirect stimuli.
- It is associated with chronic airway inflammation.
- These persist when asymptomatic and lung function is normal.
- It may normalize with treatment.
Burden of Severe Asthma
Implications of Uncontrolled Asthma (U.S.)

13.9 million
People experience asthma attacks

10.6 million
Asthma physician office visits

2.1 million
Emergency department visits

479,300
Hospitalizations

3,388
Asthma-related deaths

Higher Cost of Severe Asthma (U.S.)

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

- **Est. $56B total cost of asthma**\(^1\)
- **$12,800**
  - Increased healthcare utilization
  - Emergency Room (ER) visits
  - Hospitalizations
- **$4,800**
- **$2,200**

Patients with exacerbations have higher healthcare costs than patients without exacerbations\(^3\)

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.”

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

ERS = European Respiratory Society
ATS = American Thoracic Society

Challenges in Severe Asthma¹:
Unmet Clinical Need

- **Asthma is a heterogeneous disease** characterized by diverse symptom profiles and response to medications

- **Subset of patients remain symptomatic and experience quality of life limitations** despite standard of care medications

- **Medications have limited efficacy**, require adherence, and can have substantial side effects

- **Higher rates** of asthma exacerbations, increased steroid burden, increased morbidity and disproportionate use of healthcare resources

---

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 – Recently approved; data shows 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:


*Non-pharmacological add-on intervention

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

2. Bronchial Thermoplasty* is included as a preferred add-on treatment option in Step 5.
Bronchial Thermoplasty (BT) Delivered by the Alair™ System
What is Bronchial Thermoplasty (BT)?

• **Non-pharmacological intervention** for severe asthma that targets excess airway smooth muscle in the airways to reduce bronchoconstriction.

• **Safe, minimally invasive, outpatient** procedure performed with the Alair™ System through routine bronchoscopy

• **Clinically proven** to provide long-term reduction in severe asthma exacerbations out to at least 5 years, and improve asthma-related quality of life for patients with severe asthma*

• **Complementary treatment** to asthma maintenance medications that control inflammation
  • Not a cure for asthma or a replacement for drug therapy

*Compared to a sham-control group at one year.
BT Reduces Excess Airway Smooth Muscle (ASM)

The Alair™ System

- **Alair Catheter** – a flexible tube with an expandable wire array at the tip to deliver therapeutic RF energy to the airway walls via a standard bronchoscope

- **Alair Radiofrequency (RF) Controller** – designed to safely and accurately deliver precise, controlled RF energy through the Catheter to the airway walls
BT, Delivered by the Alair™ System
Application of RF Energy

• Temperature controlled energy (65°C) is delivered to airway wall for 10 seconds per activation

4 activations in a sub-segment
Reduced Airway Smooth Muscle

- 3 years post-treatment (canine model)¹

UNTREATED

Masson’s Trichrome stain

TREATED
BT Treatment Effect –
Airway Responsiveness to Local Methacholine Challenge

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

BT Clinical Studies
12+ years of clinical experience

**AIR2**
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**
2004-2010
- Randomized, controlled study
- N = 16
- Evaluate safety and reduction in medications and asthma symptoms in patients with severe, refractory asthma

**AIR3**
2002-2010
- Randomized, controlled study
- N = 55
- Evaluate safety and reduction in patients with moderate to severe asthma

**Feasibility**
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

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
Long-Term Clinical Outcomes out to 5 Years
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

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

2. Severe asthma classification based on treatment in Steps 5 or 6 per the NAEPP 2007 guidelines.

Pivotal U.S. study to evaluate safety and effectiveness of BT with the Alair™ System in adult patients with severe asthma.

† 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).
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

What is the Asthma Quality of Life Questionnaire

• “Gold standard” for asthma-specific disease quality of life measurement
• The AQLQ is a 32 item, disease specific questionnaire that uses standardize activities to measure limitations.
• Strong measurement properties and validity for measurements of functional impairment in people with asthma
• Patients score their experiences during the last 2 weeks on a 7 point scale (1-severe impairment to 7 –no impairment.
• A score change of 0.5 points is considered to be clinically significant and is termed the minimal important difference.
Improved Asthma-Related Quality of Life (AQLQ Score)\(^1\)

- BT group demonstrated a \textit{clinical treatment effect} over the sham group
- AQLQ score for patients treated with BT increased 1.35 over baseline through 12 months (integrated AQLQ)

![Graph showing change in AQLQ score from baseline over 12 months]

\textbf{Average Score}

- Difference in AQLQ score between groups was 0.21 (PPS=96.0%)
- Clinical treatment effect persistent across 6, 9, and 12 months

## AIR2 Respiratory Adverse Events¹,²

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\(^1\)

- **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)

Hospitalization Risk for Respiratory Symptoms Following Procedure

<table>
<thead>
<tr>
<th>Respiratory-Related Hospitalizations during Treatment Period†</th>
<th>BT (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events / Patient (%)</td>
<td>19/190 (10%)*</td>
<td>2/98 (2.0%)</td>
</tr>
<tr>
<td>Events / Bronchoscopy (%)</td>
<td>19/558 (3.4%)</td>
<td>2/292 (0.7%)</td>
</tr>
</tbody>
</table>

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

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

## Respiratory Symptoms Resulting in Hospitalization Following Procedure

<table>
<thead>
<tr>
<th>BT (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Hospitalizations in 16 Patients</td>
<td>2 Hospitalizations in 2 Patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Events (Incident Rate %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Aggravated</td>
<td>12 (6.3%)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Low FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Aspirated Prosthetic Tooth in Airway</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Asthma Aggravated</td>
<td>2 (2.0%)</td>
</tr>
</tbody>
</table>

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 5-Year 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

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)

Retention rate (from n=190) = 85.2%

Exit study

BT
Sham

AIR2 1-year
AIR2 5-year


* Exacerbations requiring treatment with systemic corticosteroids or a doubling of ICS
Rationale for Lack of Sham-Control Group after Year 1 in AIR2 Trial

- Maintaining study blind for 5 years and prohibiting further treatments for severe asthma in the sham-control group was unethical.

- Following the sham-control group after blind was broken would confound interpretation of study data, especially with expected changes in severe asthma treatments over 5 years.

- Experience from prior BT trials showed unwillingness of Control patients to continue long-term follow-up.
  - Only 50% of control patients in AIR participated in Extension Study out to 3 years.
AIR2 Extension Study
Primary Endpoint Achieved

% of Patients with Severe Exacerbations

Demonstrated durability of effect\(^1\):

- 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.

---

AIR2 5-Year Extension Study

Baseline 12-month recall (n=190)

Randomized 2:1 (n=297)

BT

Sham

Year 0 (n=190)

Year 1 (n=181)

Year 2 (n=165)

Year 3 (n=162)

Year 4 (n=159)

Year 5 (n=162)

AIR2 1-year

AIR2 5-year

Exit study

Post-hoc

AIR2 Extension Study

Post-hoc Analysis:
Average decrease over 5 years compared with 12-month baseline recall (pre-BT):

• Severe exacerbations
• ER visits for respiratory symptoms

Reduction in Severe Exacerbations Maintained out to 5 years\textsuperscript{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):

- \textbf{44\%} average decrease in percentage of patients having severe exacerbations
- \textbf{48\%} average decrease in severe exacerbation event rates

Reduction in ER Visits Maintained out to 5 years\(^1\)

- 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

No Increase in Hospitalizations over 5 Years

<table>
<thead>
<tr>
<th></th>
<th>Year prior to BT Treatment (n=190)</th>
<th>Year 1 (n=181)</th>
<th>Year 2 (n=165)</th>
<th>Year 3 (n=162)</th>
<th>Year 4 (n=159)</th>
<th>Year 5 (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of hospitalizations for respiratory symptoms</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Patients with hospitalizations for respiratory symptoms</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>percentage of Patients with hospitalizations for respiratory symptoms (%)</td>
<td>4.2</td>
<td>3.3</td>
<td>4.2</td>
<td>6.2</td>
<td>5.7</td>
<td>1.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.4, 7.1</td>
<td>0.7, 5.9</td>
<td>1.2, 7.3</td>
<td>2.5, 9.9</td>
<td>2.1, 9.3</td>
<td>0.0, 3.9</td>
</tr>
</tbody>
</table>

Note: 3 patients had 20 of the total hospitalizations (45.5%)

Lung Function (FEV$_1$)$^1$

- Pre-BD FEV$_1$ remained unchanged out to 5 Years
- Post-BD FEV$_1$ remained higher than the Pre-BD FEV$_1$ at all times
- Change between Pre-BD and Post-BD percent predicted FEV$_1$ of 8.2% at baseline and 5.9% at 5 years

Long-Term Safety Maintained out to 5 Years

• 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 FEV₁ values remained unchanged over the 5 years after BT. Post-BD FEV₁ remained higher at all times; Increase in percent predicted FEV₁ at baseline of 8.2% and at 5 years of 5.9%

Established Long-Term Effectiveness and Safety out to 5 Years\textsuperscript{1}

- **Reduction in severe asthma exacerbations requiring systemic corticosteroids**\textsuperscript{*} 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 with no increase seen in hospitalizations, asthma symptoms, or respiratory adverse events over the course of 5 years

\* or a doubling of ICS

BT Response in Allergic and Non-Allergic Patients

- No difference in the percentage of patients experiencing severe exacerbations, ER visits, asthma symptoms and hospitalizations over 5 years based on patient self-reported allergy status$^{1,2}$

Clinical Implications for Treatment of Severe Asthma

- A single BT treatment comprising of 3 procedures provides long-term benefit
- With 5 years of data demonstrating safety and clinical effectiveness, BT should be considered for adult patients with severe persistent asthma who remain symptomatic despite taking ICSs and LABAs

Bronchial Thermoplasty has become an important addition to our treatment armamentarium for severe asthma patients when standard of care medications aren’t enough.
Who are the Right Patients for BT?
Bronchial Thermoplasty 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 (ICS) and long-acting beta-agonists (LABA).
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
Precautions

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

• Post-bronchodilator FEV\textsubscript{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
Who Responds to BT?

• The AIR2 Trial was performed on patients with **severe asthma phenotype**: 79% responder rate\(^1,2\)

• Patients with **lower AQLQ or higher ACQ scores** at baseline (implying poor asthma control) responded better to BT

• Clinical response to BT in self-reported **allergic patients** (54.5%) and **non-allergic patients** (45.5%) was similar\(^2\)

**Resonder = Asthma Quality of Life Questionnaire (AQLQ) score improvement ≥ 0.5**

How BT is Performed
BT Completed in 3 Outpatient Procedures

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
Reimbursement for BT

• Providers are encouraged to seek written pre-determination for BT whenever possible prior to performing the procedure
  - Coverage policies and payment vary by payer
  - There have been approvals for BT even with a non-coverage policy
• Commercial payers starting to post positive coverage policies for their members
• Several organizations have issued statements recommending BT coverage:
  - American College of Chest Physicians (CHEST), Asthma and Allergy Foundation of America (AAFA), Allergy & Asthma Network Mothers of Asthmatics (AANMA)
• Two Category I CPT® Codes established for BT.
BT Study Publications

AIR2


RISA


AIR


Questions?