BRONCHIAL THERMOPLASTY

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Aurora Medical Group
Disclosures

- I am a paid consultant for Boston Scientific and Spiration
- Images and videos are courtesy of Boston Scientific
Overview

- What is Asthma
- Medical Management of Asthma
- Non-Medical Treatment of Asthma: Bronchial Thermoplasty (BT)
- Who are the Right Patients for Bronchial Thermoplasty?
- How BT is Performed
Asthma

• According to the National Asthma Education and Prevention Program Expert Panel Report 3 Guidelines on Asthma, “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role...In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing...These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.”
Asthma

- Airflow Obstruction is the result of multiple changes in the airways, all influenced by airway inflammation:
  - Bronchoconstriction
  - Airway Hyperresponsiveness: an exaggerated bronchoconstrictor response to a variety of stimuli, including allergens and irritants
  - Airway Edema and Mucus Hypersecretion

Diagnosis of Asthma

- Clinical Diagnosis: Wheezing, Cough, Chest Tightness, Shortness of breath
- Evidence of reversibility on spirometry
- Exclusion of alternative diagnoses
Asthma Severity

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

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Classification of Asthma Severity ≥ 12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>≤2 x/month</td>
<td>3-4 x/month</td>
</tr>
<tr>
<td>&gt;1x/week but not nightly</td>
<td></td>
</tr>
<tr>
<td>&gt;2 days/week but not daily and not more than 1x on any day</td>
<td>Daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal FEV₁/FVC:</th>
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<tbody>
<tr>
<td>8-19 yr 85%</td>
</tr>
<tr>
<td>20-39 yr 80%</td>
</tr>
<tr>
<td>40-59 yr 75%</td>
</tr>
<tr>
<td>60-80 yr 70%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interference with normal activity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Minor limitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some limitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremely limited</td>
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<table>
<thead>
<tr>
<th>Lung function</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
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<tbody>
<tr>
<td>≥2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
</tr>
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<td>Daily</td>
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<table>
<thead>
<tr>
<th>Risk</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1/year</td>
<td>&gt;2/year</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended Step for Initiating Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
</tr>
<tr>
<td>Step 2</td>
</tr>
<tr>
<td>Step 3 and consider short course of oral systemic corticosteroids</td>
</tr>
</tbody>
</table>

FEV₁ - forced expiratory volume in one second; FVC - forced vital capacity

Current stepwise approach for asthma management in patients 12 years of age or older.

BT is indicated for patients 18 years and older.
Refractory Asthma

- **Major Criteria:**
  - Treatment with continuous or near continuous (>50% of year) oral steroids
  - Requirement for treatment with high dose inhaled corticosteroids, i.e. >1260 mcg/d of beclamethasone or >880 mcg/d of fluticasone

- **Minor Criteria:**
  - Requirement for additional daily controller medication
  - Daily short acting B agonist use
  - FEV1 <80% or diurnal PEF variability >20%
  - One or more urgent care visits per year
  - Three or more oral steroid courses per year
  - Prompt deterioration with <25% reduction in inhaled or oral steroid dose
  - Near fatal asthma event in past

Implications of Uncontrolled Asthma

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

Challenges in Severe or Refractory Asthma

- 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 serious side effects.
- Patients with severe asthma experience higher rates of asthma exacerbations, increased morbidity and disproportionate use of healthcare resources.
Higher Cost of Severe Asthma

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

Est. $56B total cost of asthma\(^1\)

<table>
<thead>
<tr>
<th>Cost/Patient/Year</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>$2,200</td>
<td></td>
<td>$4,800</td>
<td>$12,800</td>
</tr>
</tbody>
</table>


\(^3\) American Lung Association, Trends in Asthma Morbidity and Mortality, February 2010 report.
Current stepwise approach for asthma management in patients 12 years of age or older.

BT is indicated for patients 18 years and older.
What is Bronchial Thermoplasty (BT), Delivered by the Alair™ System?

- **Safe, minimally invasive, outpatient bronchoscopic procedure** for the treatment of severe asthma:
  - Performed as 3 separate bronchoscopy procedures
  - Delivers controlled radiofrequency energy to the airway walls to reduce excessive airway smooth muscle, which limits the muscle’s ability to constrict the airways

- **Clinically proven** to provide long-term reduction in 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 by targeting ASM bronchoconstriction
  - Not a cure for asthma or a replacement for drug therapy

*Compared to a sham-control group at one year.
Role of Airway Smooth Muscle (ASM) in Asthma

Airway of Normal Patient

Asthma Attack
Bronchial Thermoplasty – Reduces Excess ASM

Reduce Airway Smooth Muscle (ASM) → Reduce Broncho-constriction → Reduce Asthma Exacerbations → Improve Asthma Quality of Life
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)

UNTREATED

TREATED

Masson’s Trichrome stain
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

- **2005-2012 AIR2 TRIAL**
  - Randomized, double-blind, sham-controlled multi-site, pivotal IDE study to evaluate effectiveness and safety in patients with severe persistent asthma.
  - $n = 190$

- **2004-2010 RISA TRIAL**
  - Randomized, controlled trial to evaluate safety and reduction in medications and asthma symptoms in patients with severe, refractory asthma.
  - $n = 16$

- **2002-2010 AIR TRIAL**
  - Randomized, controlled trial to evaluate effectiveness and safety in patients with moderate to severe asthma.
  - $n = 55$

- **2000-2007 FEASIBILITY STUDY**
  - Nonrandomized, prospective study to examine safety of BT over a 2-year period.
  - $n = 16$

‡Asthma Intervention Research (AIR)
§Research in Severe Asthma (RISA)
Asthma Intervention Research 2 (AIR2) Trial

• **Purpose:** Pivotal U.S. Investigational Device Exemption (IDE) Study to evaluate the safety and effectiveness of BT with the Alair™ System in patients with severe asthma
• **Multicenter, randomized, double-blind, sham-controlled**
• **Study Population:**
  - Severe persistent asthma (297 patients)
  - Symptomatic despite high dose ICS + LABA
  - **Primary Endpoint:** Asthma Quality of Life Questionnaire (AQLQ) score
• **Secondary Endpoints:** Severe exacerbations, ER visits, days lost from work/school/other daily activities due to asthma symptoms
• **Follow-up:** One year
Demonstrated Clinical Effectiveness at 1 Year

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

PPS = Posterior Probability of Superiority

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 during the treatment period (first BT treatment to 6 weeks following third BT treatment)
  - Typically occurring within one day and resolving within one week with standard care

- Fewer respiratory adverse events and ER visits in the BT group in the posttreatment period (6 weeks after final 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&lt;sup&gt;a&lt;/sup&gt;</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.

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

Respiratory Symptoms Resulting in Hospitalization Following Procedure\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>BT (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events (Incident Rate %)</td>
<td>19 Hospitalizations in 16 Patients</td>
<td>2 Hospitalizations in 2 Patients</td>
</tr>
<tr>
<td>Asthma Aggravated</td>
<td>12 (6.3%)</td>
<td>Asthma Aggravated</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>3 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Low FEV(_1)</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Aspirated Prosthetic Tooth in Airway</td>
<td>1 (0.5%)</td>
<td></td>
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High Patient Satisfaction with BT

- Majority of AIR2 Trial patients reported at 1 year that they would do BT again and would recommend the treatment to a friend or family member\(^1\)

- 97% of BT patients would recommend BT to a friend or family member.

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AIR2 Trial and AIR2 Extension Study

**AIR2 Trial**

**Objective:**
Superiority vs. Sham

**Primary Endpoint:**
AQLQ
BT vs. Sham at 1 year

**Baseline Assessments Including Prior 12 Month History**

**Randomization**

**Double-blinded**

**BT Group**
3 bronchoscopies (n=190)

**Sham Group**
3 sham bronchoscopies (n=98)

**Quarterly and Annual In-office Follow-up until end of Year 1** (n=181 for BT; n=97 for Sham)

**AIR2 Extension Study**

**Objective:**
Durability of effect

**Primary Endpoint:**
% of patients with severe exacerbations*
BT at years 2-5 vs. BT at 1 year

**BT Group ONLY**

**Quarterly Phone Contact and Annual In-office Follow-up for 5 Years** (n=162 at Year 5)

* Exacerbations requiring treatment with systemic corticosteroids
AIR2 Trial 5-Year Extension Study

Durability of Effectiveness

- **Objective:** Evaluate *durability of effectiveness and safety* of BT to 5 years in patients with severe persistent asthma.

- **Hypothesis:** The percentage of patients experiencing severe exacerbations in Years 2-5 is *not substantially worse* than in the first year.

- **Primary Endpoint:** The percentage of patients experiencing severe exacerbations during subsequent 12-month periods out to 5 years compared with the percentage of patients who experience severe exacerbations during the first year after BT treatment with the Alair™ System.
  - The non-inferiority margin was established as the upper 95% confidence limit of the difference in proportions in each year minus Year 1 to be less than 20%.

- **Secondary Endpoints:**
  - Emergency room (ER) Visits for respiratory symptoms
  - Hospitalizations for respiratory symptoms
  - Respiratory adverse events
  - Lung function (Pre- and Post-BD FEV₁)
AIR2 Extension Study Patient Retention Rate > 85%

<table>
<thead>
<tr>
<th>No. of BT patients completing follow-up at:</th>
<th>BT</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Months</td>
<td>181</td>
</tr>
<tr>
<td>2 Years</td>
<td>165</td>
</tr>
<tr>
<td>3 Years</td>
<td>162</td>
</tr>
<tr>
<td>4 Years</td>
<td>159</td>
</tr>
<tr>
<td>5 Years</td>
<td>162</td>
</tr>
</tbody>
</table>

- Retention rate from original 190 patients treated = 85.2%
- Retention rate from patients entering long-term follow-up = 89.5%
Reduction in Severe Exacerbations Maintained out to 5 years

- The reduction in severe exacerbations requiring systemic corticosteroids at 1 year (vs. sham-treated patients) 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\textsuperscript{1}

- The reduction in ER visits for respiratory symptoms at 1 year (vs. sham-treated patients) 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

Established Long-Term Effectiveness and Safety out to 5 Years

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

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

- No clinically significant deterioration in lung function ($\text{FEV}_1$) at 5 years

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 ($\text{FEV}_1$)

No clinically significant deterioration at 5 years

- 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

BT Effective in Allergic and Non-Allergic Patients

- There was 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 (steps 5 and 6 of the NAEPP EPR3 asthma guidelines)

Bronchial Thermoplasty has become an important addition to our treatment armamentarium for severe asthma patients when standard of care medications aren’t working.
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).

Reference the Alair Bronchial Thermoplasty System Directions for Use for more information.
How We Do It

• Office visit to confirm the diagnosis of asthma and ensure alternative diagnoses have been “ruled out”.
• Typically, this will include full PFT, high resolution chest CT, CBC, IgE, alpha one antitrypsin.
• Ensure medical compliance and that any asthma triggers can be removed.
• Ensure patient is significantly impacted by his/her asthma
• In depth discussion regarding the pros and cons of the procedure and to establish expectations. Even though we have 5 year data, I continue to emphasize the uncertainty of the long term effect
AIR 2 Inclusion Criteria

- Age 18-65
- Documented asthma requiring inhaled corticosteroids (>1000 mcg/d beclamethasone equivalent) and long acting β agonist (>100 mcg /d salmeterol equivalent)
- Oral steroids less than 10 mg/day
- Stable doses of Omalizumab for the last year if used
- Stable asthma symptoms for the four weeks prior to study entry
- Prebronchodilator FEV1 greater than or equal to 60% or positive methacholine challenge test with PC20 < 8 mg/ml
- Less than 10 pack year tobacco history
AIR 2 Exclusion Criteria

- Life threatening asthma
- Chronic sinus disease
- Other respiratory diseases such as emphysema or chronic bronchiectasis
- Use of immunosuppressants, anticoagulants or beta-blockers
- Three or more hospitalizations for asthma
- Three or more lower respiratory tract infections
- More than 4 courses of oral corticosteroids in the year prior to enrollment.
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 (relative)
- Patients that have previously been treated with the Alair™ System

Reference the Alair Bronchial Thermoplasty System Directions for Use for more information.
How We Do It

- Prior authorization
- Delay the procedure if active infection or alterations in asthma control over the last two weeks prior to the scheduled procedure
- Prophylactic OCS (50mg/day) administered 3 days prior, day of and day after procedure
- Morning of the procedure, pre-operative spirometry with bronchodilator
- Treatment with an antisialogogue, i.e. glycopyrrolate and bronchodilator
- Performed under general anesthesia
BT is performed by a trained pulmonologist in 3 outpatient visits, typically scheduled 3 weeks apart.
Post-Procedure/Patient Follow Up

- Post-operative spirometry with bronchodilator approximately 4 hours after
- Once discharged, patient encouraged to call with any issues
- Office visit at 2 weeks to assess clinical stability and schedule subsequent BT procedures as appropriate
- After completion of all three BT treatments, patient returns to primary asthma physician for long term asthma management
- I continue to see patient at 3, 6, and 12 months with spirometry with bronchodilator. If patient will allow, I follow yearly thereafter with PFT.
- Patient may be evaluated for step-down therapy to determine lowest level of medication necessary to maintain asthma control
Clinical Case

- 32 yo female with asthma and GERD.
- Triggers include any perfumes, air fresheners, hand sanitizers, cleaning supplies, exercise, and cold air. She is profoundly limited in her day to day activities.
- In the year prior to presentation, 5 urgent care visits, 3 courses of oral prednisone, rescue inhaler use 3 times per day, nocturnal awakenings 2x/week.
- Medications include symbicort 160/4.5 two puffs bid, Qvar 80 mcg two puffs daily, singulair, albuterol nebulizer
- Autism therapist with home visits as mandatory part of her job. Repeatedly has missed work.
Clinical Case

- Nonsmoker
- Prior allergy testing was normal
- Normal IgE level
- Full PFT, high resolution CT, CBC normal
- Methacholine challenge test positive at 0.25 mg/ml dose previously
- Laryngoscopy normal without evidence of vocal cord dysfunction
Clinical Case

- Underwent Bronchial Thermoplasty:
  - RLL 121 activations
  - LLL 129 activations
  - BUL 163 activations

- At 6 month visit, able to watch first movie in theater and “had her hair done” at a salon.

- At two years, PFT remain normal, no exacerbations requiring steroids, rare rescue inhaler use, maintenance asmanex 220 mcg one inhalation every day.
Questions?

• Please contact me at:
  • Email: Steven.leh@aurora.org
  • Office: 414.385.2344
  • Fax: 414.649.7819

Boston Scientific Website: www.BTforAsthma.com
More Treatment Options Needed When Medications Aren’t Working

- **Existing Drug Therapies**
  - **Severity of Asthma**
  - **Alternatives needed**
    - **5** Oral Corticosteroids +/- Anti IgE treatment: Severe
    - **4** Medium or high-dose ICS + LABA +/- Leukotriene modifier +/- sustained release theophylline: Severe
    - **3** Low-dose ICS + Long-acting Beta2-agonists (LABA) or Medium-dose ICS or Low dose ICS + Leukotriene modifier: Moderate
    - **2** Low-dose Inhaled Corticosteroids (ICS) Leukotriene modifier: Moderate
    - **1** Short-acting Beta2-agonists (SABA): Mild