SEVERE ASTHMA 2015

Big Sky Pulmonary Conference
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AND THE ROLE OF BRONCHIAL THERMOPLASTY

RICK BLEVINS, MD

- No financial disclosures
- Asthma
  - Severe Asthma
  - Bronchial Thermoplasty

SEVERE ASTHMA: WHAT IS IT?

Patients who require high dose ICS or continuous or near continuous oral steroid treatment to maintain control (ERS/ATS)

Patients who have frequent and severe asthma symptoms and airflow limitation, but are not on asthma controller medication (NH/VGINA)

Severe asthma (ATS) usually requires high doses of controller meds to maintain control; asthma is usually “not well controlled” or “very poorly controlled” by NIH/GINA criteria

Usual Goals of asthma treatment may not be possible in severe asthma:
Prevention of chronic and severe symptoms; Normalize pulmonary function; Normal activity levels; Prevent exacerbations; Improve Q of Life; Minimal medication side effects
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 asthma¹

ERS = European Respiratory Society
ATS = American Thoracic Society


ERS/ATS DEFINITION OF SEVERE ASTHMA

The definition of severe asthma requires that one or both of the following levels of treatment for the previous year has been needed to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this level of treatment:

- Moderate or low-dose inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA) for the previous year
- Treatment with systemic glucocorticoids for 10% of the year

Uncontrolled asthma is defined as at least one of the following:

- Four or more exacerbations resulting in oral corticosteroids for 14 days or more (often labeled as NAEPP-EPR guidelines)
- Frequent severe exacerbations: two or more hospitalizations (including those with oral corticosteroids for 14 days or more) in the previous year
- History of serious exacerbations, at least one hospitalization, intensive care unit stay, or withdrawal of treatment in the previous year
- Absent improvement after exacerbation treatment with oral steroids and/or LABA or LAMA for at least 10% of the year

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


HIGHER COST OF SEVERE ASTHMA
(U.S.)

Higher healthcare costs with asthma severity²

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


SEVERE ASTHMA: HOW COMMON?

Asthma increasing incidence: about 7% of US population

Severe Asthma: 5-10% of asthma population

US population 320 million
23 million asthmatics
1.2-2.3 million severe asthmatics

Montana population 1 million
70,000 asthmatics
6000 severe asthmatics
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
- **3,888** Asthma-related deaths

ASTHMA HETEROGENEITY

Increasing recognition that asthma is a complex condition with several underlying pathologies that develop as consequence of a variety of gene-environment interactions causing multiple clinical phenotypes.

No uniform response to various meds, especially steroids and other anti-inflammatory/cytotoxic drugs. Specific phenotypes probably exist, but poorly defined. Xolair (omalizumab) IgE monoclonal antibody only 30% of allergic asthmatics respond.

Methotrexate, gold, cyclosporine, IVIG all have widely variable responses supporting the likelihood of subtypes.

ASTHMA HETEROGENEITY

Is severe asthma a distinct disease or part of the asthma spectrum? Does it present de novo, or develop over time from mild disease? Can have early onset or late onset. Hospitalization/ICU can be the first presentation with no previous history of mild disease. Remodeling occurs over time, but does it occur over a shorter time frame as well?
NATURAL HISTORY OF ASTHMA

Poorly Studied
Not well described
Wheezing in young children below age 6 probably benign and resolves. A subgroup will have persistence and eventual asthma atopic state; early onset of severe symptoms, maternal history of asthma and maternal smoking frequently found.
Wheezing and asthma in adolescence associated with persistence into adulthood, but unusual to worsen over time.
Children with more severe symptoms have lower lung function than those with less severe symptoms.
Deficits in PFT established by age 6-7 and persists into adult life.
Adults with wheezing more likely than children to have persistent asthma and loss of lung function.
Children and adults with severe asthma or difficult to control asthma continue to have uncontrolled asthma and decline in PFT with age despite maximal medical therapy.

SEVERE ASTHMA: EVALUATION

Evaluate comorbidities:
- Chronic rhinosinusitis
- GERD
- Smoking
- Obesity
- Obstructive Sleep Apnea
- Psychiatric disorders
Evaluate for conditions that mimic asthma
Remember vocal cord dysfunction

SEVERE ASTHMA MIMICS

- Vocal Cord Dysfunction (VCD)
- Central airway obstruction
- COPD
- Bronchiectasis
- Allergic Bronchopulmonary Aspergillosis (ABPA)
- Bronchiolitis
- Hypereosinophilic obliterative bronchiolitis
- Cryptogenic organizing Pneumonia (COP)
- Hypersensitivity pneumonitis
- Churg-Strauss
- Asthmatic granulomatosis
- Sarcoidosis
- Cardiac disease
SEVERE ASTHMA: TREATMENT

2007 NIH Guidelines/GINA guidelines

Evaluate medication compliance: every visit
- proper use of inhalers?
- frequently
- proper medication?
- altered after hospitalization
- refill rates from pharmacy data
- ask the family

Evaluate for environmental exposures
- secondary tobacco smoke
- pets
- workplace exposures
- home exposures/allergens
- medications? Beta blockers, including eye drops

INITIATION OF TREATMENT

NIH GUIDELINE STEP THERAPY
SEVERE ASTHMA: ALTERNATIVE AND EXPERIMENTAL AGENTS

ANESTHETIC AGENTS for status asthmaticus
- Inhalational: halothane, isoflurane, enflurane, sevoflurane
- IV: ketamine
Nebulized furosemide: small studies, small benefit

CHRONIC SEVERE ASTHMA
- Tiotropium (Spireva): better than double beclomethasone, not inferior to addition of salmeterol
- Nebulized lidocaine: small studies show benefit
- Nebulized heparin: may have anti-inflammatory effects and some benefit. Current studies ongoing

IMMUNE MODULATORY THERAPY
- Methotrexate: modest increase in FEV1, decrease in steroid dose
- Gold: small decrease in steroid dose, high toxicity
- Cyclosporine: small decrease in steroid dose, some toxicity; aerosolized cyclosporine being studied
- Colchicine: mixed results. Small improvements at best
- Hydroxychloroquine: conflicting results
- Immunoglobulin: no sig. benefit in several large trials
- Dapsone: small study with significant decrease in steroid dose but sig. anemia. No RCT, no reliable evidence to support
- Macrolid antibiotics: both antimicrobial and antiinflammatory
  Some asthmatics have chlamydia or mycoplasma pneumoniae
  Multiple studies found no sig. difference, but may be a subgroup of noneosinophilic asthma benefit

ANTI TNF-ALPHA AGENTS
- Remicade (infliximab)
- Simponi (golimumab)
- Enbrel (etanercept)
Large trials fail to show reduction in exacerbations or other therapies or improvement in lung function.
Currently no evidence of beneficial effect in severe asthma
SEVERE ASTHMA: ALTERNATIVE AND EXPERIMENTAL TREATMENT

Antifungal therapy: RCT with itraconazole showed improved AQLQ, peak flow, and total IgE after 32 weeks. But results not sustained after stopping no improvement after 3 months of voriconazole

Biofeedback: training in heart rate variability resulted in decreased med use, decreased symptoms and improved pulmonary function

Breathing exercises: prolong exhalation and decrease minute ventilation can improve control

Physical training: increase in MVO2 and Q of L

Dietary alterations: Omega 3 FA—may benefit EB

No demonstrated benefit: Antioxidants (vit C & vit E) Vitamin D Elimination Diets Magnesium

Non pharmacologic Interventions: evidence limited by small number and size of well designed trials. Generally insufficient data to recommend as useful adjunct

acupuncture massage therapy herbal medications chiropractic manipulation speleotherapy (cave or mine therapy) halotherapy (dry aerosol microparticles of salt or minerals to simulate salt mines)
ANTI-INTERLEUKIN 5 (IL-5) ANTIBODIES

- IL-5 is a potent recruiter of eosinophils to airways
- Anti-IL-5 monoclonal Ab may be beneficial in subset of uncontrolled asthma, and persistent eosinophilia
- Mepolizumab-recent studies show reduction in steroid dose, decrease exacerbations and improved control compared to placebo.
- Reslizumab-fewer studies, improvement less robust
- Both are IV or SQ
- Mepolizumab currently being evaluated by FDA
GINA Stepwise Approach to Control Symptoms and Minimize Future Risk:


2. INTERVENTION AVAILABLE WHEN MEDICATIONS ARE NOT ENOUGH

   - GINA Stepwise Approach to Control Symptoms and Minimize Future Risk

   - 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

3. BRONCHIAL THERMOPLASTY (BT)

   DELIVERED BY THE ALAIR™ SYSTEM

   - WHO 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)

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


REDUCED AIRWAY SMOOTH MUSCLE

- 3 years post-treatment (canine model)

Masson’s Trichrome stain

UNTREATED 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

- 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

**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%)

**AIR2 RESPIRATORY ADVERSE EVENTS**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Period (&lt;12 weeks)</th>
<th>Post-Treatment Period (&lt;46 weeks)</th>
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</thead>
<tbody>
<tr>
<td>Asthma (Multiple Symptom)</td>
<td>BT (N=190) %</td>
<td>Sham (N=98) %</td>
</tr>
<tr>
<td></td>
<td>52.1%</td>
<td>27.3%</td>
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<tr>
<td>Wheezing</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
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<td></td>
<td>15.3%</td>
<td>4.3%</td>
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<tr>
<td>Atelectasis</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
</tr>
<tr>
<td></td>
<td>4.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
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<tr>
<td></td>
<td>3.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
</tr>
<tr>
<td></td>
<td>7.9%</td>
<td>3.2%</td>
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<tr>
<td>Upper Respiratory Tract Infection</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
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<td>20.0%</td>
<td>29.9%</td>
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<tr>
<td>Nasopharyngitis</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
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<td></td>
<td>4.7%</td>
<td>7.1%</td>
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<tr>
<td>Throat irritation</td>
<td>BT (N=187) %</td>
<td>Sham (N=98) %</td>
</tr>
<tr>
<td></td>
<td>4.7%</td>
<td>12.2%</td>
</tr>
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</table>

*Posterior Probability of Superiority (PPS) >95.0%

HIGH PATIENT SATISFACTION WITH BT

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


AIR2 TRIAL 5-YEAR EXTENSION STUDY

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

AIR 5-YEAR EXTENSION STUDY

- Objective:
  - Durability of effect
- Primary Endpoint:
  - % of patients with severe exacerbation at Years 2, 3, 4, and 5:
- Non-inferior to Year 1
- Secondary Endpoints:
  - Severe exacerbations, ER visits for respiratory symptoms, lung function (Pre-BD FEV1), Respiratory adverse events

ESTABLISHED LONG-TERM EFFECTIVENESS AND SAFETY OUT TO 5 YEARS

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

* or a doubling of ICS

References:

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%.

References:

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.

References:
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?

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

**HOW BT IS PERFORMED**

**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 COMPLETED IN 3 OUTPATIENT PROCEDURES

BT is performed by a BT-certified pulmonologist in 3 outpatient visits, typically scheduled 3 weeks apart.

APPLICATION OF RF ENERGY

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

BT-WHO SHOULD BE CONSIDERED?

- Intermittent or continuous oral corticosteroids less than 10 mg daily and/or high dose ICS/other controllers
- FEV1 greater than 60% of predicted and within 10% of best value on day of procedure
- No severe asthma exacerbation within 4 weeks
- No life-threatening exacerbation within past year
BT-A TYPICAL REFERRAL

1. FEV1 35-60% of predicted
2. Daily steroids 20-60 mg daily plus high dose ICS/other controllers
3. Frequent exacerbations requiring oral steroid boost and hospitalization
4. Intubated within past several years for respiratory failure
5. Very poor quality of life

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 FEV1 < 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 comorbidities, 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:
  - 4 or more lower respiratory tract infections (LRTI)
  - 3 or more hospitalizations for respiratory symptoms
  - 4 or more OCS pulses for asthma exacerbation

Reference the Alair™ Bronchial Thermoplasty System Directions for Use for more information.

BT-CURRENT ISSUES

1. Expensive. $15-25K for each patient
2. Insurance coverage. Many still consider it experimental despite FDA approval April 2010 and endorsement by asthma professional org.
3. Controversy. Methods and results of studies leading to approval criticized
4. Some patients failed to improve. Need to identify phenotype of positive responders
5. Patients outside the recommended parameters have not been extensively studied: this includes those with the severest asthma
6. Consensus: Need an active registry to collect data on safety and efficacy as more are done.
CARDIAC ABLATION FOR ATRIAL FIBRILLATION

Covered Information
- Not a cure
- Treatment for refractory symptoms only
- High 5 year recurrence rate
- Small chance of pulmonary vein stenosis after treatment
- Accepted by and claims paid by most insurance

BRONCHIAL THERMOPLASTY: EDITORIAL CONTROVERSY

- Exclusion of patients with the most severe asthma
- Analysis of results and statistical results
- Criticism that primary endpoint of improved quality of life highly influenced by a large placebo effect
- Failure to reach statistical significance in secondary endpoints: improved PFT, goals of asthma therapy
- Criticism that unscheduled office visits, ED visits, and hospitalizations were all interlinked: Study not adequately powered and not a primary or secondary endpoint of the AIR-2 Trial
- Criticism that the sham arm was not studied for 5 years: how do we know the 1 year result maintained

BRONCHIAL THERMOPLASTY POSITION STATEMENTS

California Technology Assessment Forum (CTAF)
Use of BT for treatment of severe refractory asthma meets Criterion 1-5 for safety, effectiveness and improvement in net health outcomes.

Global Initiative for Asthma (GINA): BT is add on therapy option for selected symptomatic patients who are at step 5

British Thoracic Society (BTS): BT is option for selected poorly controlled asthma at step 4-5 of guidelines.
CHEST believes that based on the strength of the clinical evidence, bronchial thermoplasty offers an important treatment option for adult patients with severe asthma who continue to be symptomatic despite maximal medical treatment and, therefore should not be considered experimental. RCT of BT for severe asthma have shown a reduction in the rate of severe exacerbations, ER visits and days lost from school or work. Additionally, data published in Dec. 2013 demonstrates the persistence of the reduction in asthma symptoms for at least 5 years.

**BT-BENEFIS EXPERIENCE**

- 6 patients treated
- No hospitalizations or complications from procedures
- Reduction in exacerbations
- Improved quality of life in first 5: too soon to know in 6th
- No improvement in spirometry, consistent with expectations from studies
- Reduction in medications, including steroids.
- Registry in progress

**CONCLUSIONS**

BT is add on therapy to improve symptoms in severe asthma. Not a cure

Should be considered in appropriate candidates but insurance approval slow in coming: BCBS just published a policy

Consider referral for Patients meeting severe or poorly controlled asthma definition

Robust registry and data collection required to identify the phenotype of responders and evaluate long term results
BT-CAN IT BE SAFELY DONE IN MORE SEVERELY IMPAIRED ASTHMATICS?
J ASTHMA 2013 MARCH: 50(2)

- 8 patients, severe asthma, poorly controlled despite step 5 therapy
- Mean Fev1 51.8% predicted
  - 5/8 patients with Fev1 < 50% predicted and mean Fev1 37.4% predicted
- Mean number hospitalizations for asthma in 1 year prior to BT 2.9
- Average prednisone dose before BT 27.5 mg/day
- No unexpected adverse events
- No deaths or need for post procedure vent support

SEVERE ASTHMA

- QUESTIONS?
- Physicians doing bronchial thermoplasty in Great Falls
  - Rick Blevins, MD
  - Holly Strong, MD
  - John Mazur, MD
  - Dave Anderson, MD