

# ***New and Emerging Technologies for the Treatment of Asthma***

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## ***Overview:***

- ▶ Asthma statistics and cost
- ▶ Asthma demographics
- ▶ Current treatment standards of treatment for asthma
- ▶ The role of eosinophils and neutrophils in asthma
- ▶ Emerging pharmacotherapy for asthma
- ▶ An emerging therapeutic option–Bronchial Thermoplasty
- ▶ Summary

## **Asthma: Current Statistics**

- ▶▶ Increasing prevalence, cost and utilization rates

### **Asthma Statistics**

- ▶ Worldwide over 300 million people have asthma
- ▶ In the US there are 20 million asthmatics
  - 6.7 million children<sup>1</sup>
  - 16.2 million adults<sup>2</sup>
- ▶ Prevalence:
  - 9.1% in children<sup>1</sup>
  - 7.3% in adults<sup>2</sup>

<sup>1</sup>Source: *Summary Health Statistics for U.S. Children: National Health Interview Survey, 2007, table 1* <http://www.cdc.gov/nchs/fastats/asthma.htm>

<sup>2</sup>Source: *Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2007, tables 3, 4* <http://www.cdc.gov/nchs/fastats/asthma.htm>

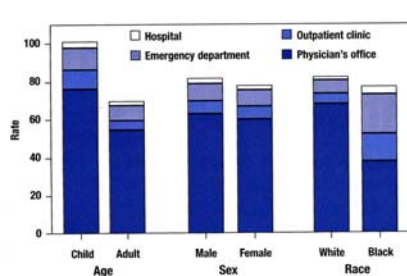
## Asthma Cost Statistics<sup>1</sup>

- ▶ Costs depend on severity of disease and extent of exacerbation and control
- ▶ Annual asthma cost in the US is estimated at:
  - \$9.4 Billion in direct medical costs
  - \$4.6 Billion in indirect cost
- ▶ Of the medical cost:
  - 50% is for rescue or emergency treatment
  - 33% is for medication

<sup>1</sup> Moorman JE, Rudd RA, Johnson, CA; *National Surveillance for States 1980-2004; MMWR Surveillance Summary 2007*

## Asthma Utilization

- ▶ For the 3 years 2001-03 there were:
  - 12.3 million office visits
  - 1.3 million hospital OP visits
  - 1.8 million ED visits
  - 504,000 hospital discharges

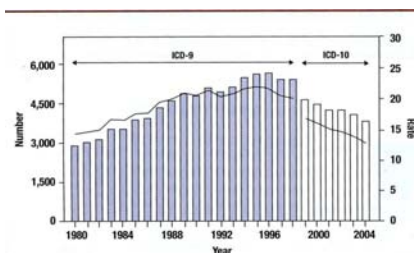


\*Per 100 persons with current asthma.

Moorman et al, 2007.<sup>1</sup>

## Asthma Death Rates

- ▶ Asthma death rates from 2000 to 2004 were over 4,000 per year
- ▶ About half occurred in persons over 65.
- ▶ 200 were in children under 18



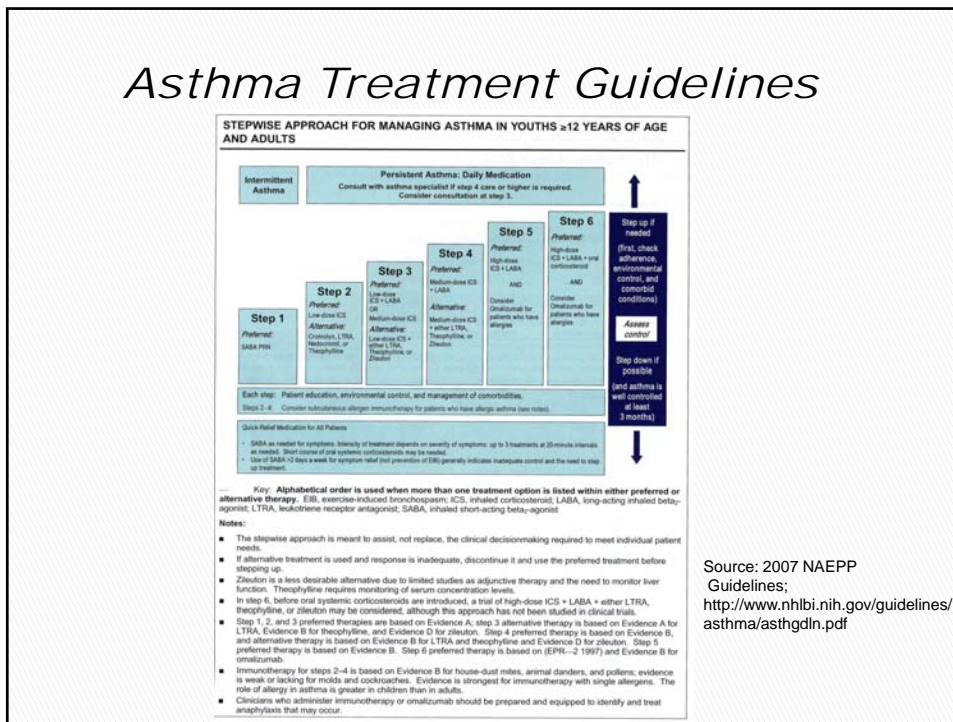
National Vital Statistics System, National Center for Health Statistics.  
 \*Per million population. Age-adjusted to 2000 U.S. population.  
 †During 1979-1998, ICD-9 was used to classify deaths. In 1999, ICD-10 was implemented.

Moorman et al, 2007.<sup>1</sup>

## Current Standards of Asthma Treatment

- » Treating according to guidelines

# Asthma Treatment Guidelines



## The Role of Eosinophils and Neutrophils

» Insights from Clinical Studies

## ***Eosinophils : Role in Asthma***

- ▶ Increased numbers of eosinophils in peripheral blood and in airway secretions are a characteristic feature of asthma.
- ▶ Eosinophils are typically higher in number in patients some with severe asthma.
- ▶ Eosinophilic asthma is a distinct phenotype:
  - Associated with thickening of the basement membrane
  - Corticosteroid responsive

Fahy, John V.; Eosinophilic and Neutrophilic Inflammation In Asthma; *Proc. Am. Thorac. Soc.*; Vol 6. pp 256-259, 2009

## ***Neutrophils: Role in Asthma***

- ▶ In some severe asthmatics, neutrophils are prominent in airway secretions during acute exacerbations.
- ▶ The neutrophils may have roles in both the initiation and the resolution of the attack.
- ▶ Generally asthma associated with neutrophils:
  - Does not show basement membrane thickening
  - Tends to have more severe airway obstruction
  - Is relatively corticosteroid resistant
- ▶ The relationship of cellular inflammatory markers and neutrophils shows promise to better understand individual patient differences.

Fahy, John V.; Eosinophilic and Neutrophilic Inflammation In Asthma; *Proc. Am. Thorac. Soc.*; Vol 6. pp 256-259, 2009

## ***Inflammatory Mediators***

- ▶ There is increasing awareness of the role of CD4 T cells in allergic diseases and recent new knowledge about Th1 and Th2 subsets.
- ▶ T-cells in the airways of asthmatics have cytokine profiles characteristic of Th2 cells.<sup>1</sup>
- ▶ IL-13 is a key effector cytokine secreted by Th2 cells and is a potent inducer of an asthma phenotype in mouse models.<sup>2</sup>
- ▶ Studies also show that epithelial cells can respond to environmental stimuli in ways that affect CD-4 T cells and the accumulation of mast cells and eosinophils.<sup>2</sup>

1. Mosman TR, Cherwinski,H, Bond MW, Giedlin MA, Coffman RL;  
*J Immunol*; 1986, 13: 2348-2357

2. Fahy, John V.; Eosinophilic and Neutrophilic Inflammation In Asthma; *Proc. Am. Thorac. Soc.*; Vol 6. pp 256-259, 2009

## ***Asthma: Potential Directions for Pharmacotherapy***

- ▶▶ New therapies based on inflammatory mediators are being explored

## ***Pharmacotherapy Updates***

- ▶ Pipeline agents and potential new targets:
  - Additional combination treatments: e.g. Mometasone/formoterol , fluticasone/formoterol
  - Sublingual immunotherapy
  - Cytokine antibodies (IL-8, IL-13)
  - CXCR-2 agents
  - Anti IL-5, Mepolizumab
  - Anti-TNFs in asthma
  - C-Kit inhibitors
  - Thymic Stromal Lymphopoietin (TSLP)

## ***Interleukin-8***

- ▶ IL-8 is a chemokine produced by macrophages and other cell types such as epithelial cells.
- ▶ Primary function of IL-8 is chemotaxis in its target cells such as neutrophils.
- ▶ IL-8 is bound numerous surface receptors, with the most studied being the G-protein coupled serpentine receptors (CXCR1, CXCR2).
- ▶ CXCR2 antagonists can decrease neutrophil migration and may have a role in neutrophilic asthma exacerbations.

## ***Interleukin-13***

- ▶ Cytokine secreted by T-helper type 2 cells, an important mediator of allergic inflammation.
- ▶ Most of the biological effects of IL-13 are mediated via a single transcription factor, signal transducer and activator of transcription 6 (STAT6)
- ▶ IL-13 induces many features of allergic lung disease including airway hyperresponsiveness, goblet cell metaplasia and mucus hypersecretion
- ▶ However, so far, IL-13 antagonists have not produce significant results in asthma

## ***Interleukin-5***

- ▶ The IL-5 receptor belongs to the type 1 cytokine receptor family. Consists of 2 polypeptide chains
  - $\alpha$  subunit binds IL-5 and confers the receptor specificity
  - $\beta$  subunit contains the signal transduction domains
- ▶ Mepolizumab is a humanized monoclonal antibody to IL-5 that may improve that may improve eosinophilic asthma.
- ▶ Mepolizumab inhibits the growth of eosinophils in asthma where these cells are overexpressed.

## ***TNF $\alpha$ and Asthma***

- ▶ TNF $\alpha$  levels were found to be increased in broncioalveolar lavage fluid of asthmatics.
- ▶ Likewise TNF $\alpha$  gene expression was increased in asthmatics.
- ▶ 17 subjects were treated with etanercept and there was associated improvement in one open label study.<sup>1</sup>

1. Howarth, PH et al; *Thorax*; 2005; 60: 1012-1018

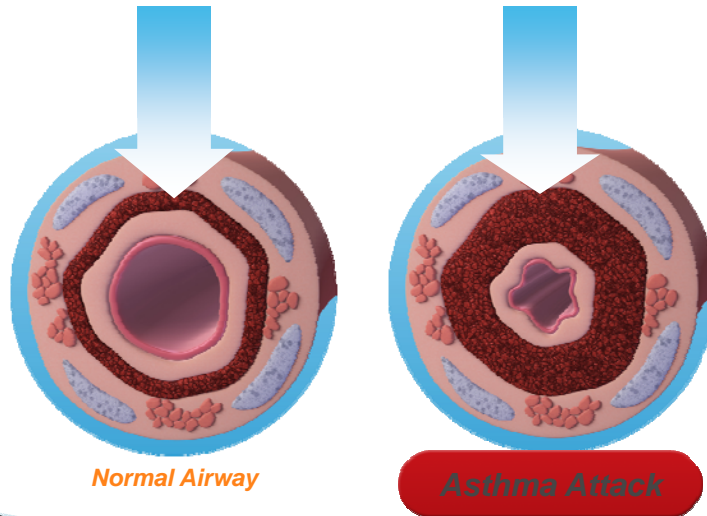
## ***C-Kit and TSLP***

- ▶ C-Kit: ( A cytokine receptor on hematopoetic stem cells) However, when agents like Gleevec are given, mast cells decrease and virtually disappear. This receptor is in early investigation for potential use in asthma.
- ▶ TSLP (Thymic Stromal Lymphopoetin) is a gene that encodes a hematopoetic cytokine that induces the release of T-cell attracting cytokines. Expression of TSLP is enhanced under asthma like conditions. Blocking the production of TSLP may be able to prevent or treat asthma exacerbations

## ***Bronchial Thermoplasty***

- » The role of airway smooth muscle in asthma pathophysiology

### ***Airway Smooth Muscle***



### ***What is Bronchial Thermoplasty?***

- ▶ A means to deliver thermal energy to the airways via a bronchoscope to reduce airway smooth muscle
- ▶ Outpatient procedure

### ***Why Bronchial Thermoplasty***

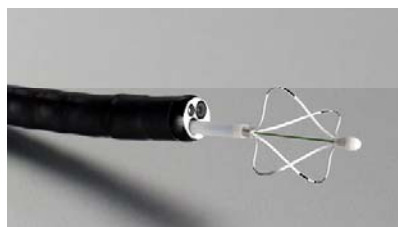
- ▶ Unmet needs in severe asthma
  - Patients not adequately controlled despite available medications
  - Significant negative impact on quality of life
  - High health care costs

## ***Why Bronchial Thermoplasty***

- ▶ Anti-inflammatory treatments (inhaled corticosteroids) remain a key component of care.
- ▶ However, airway constriction that leads to asthma exacerbations is primarily caused by airway smooth muscle (ASM) contraction.

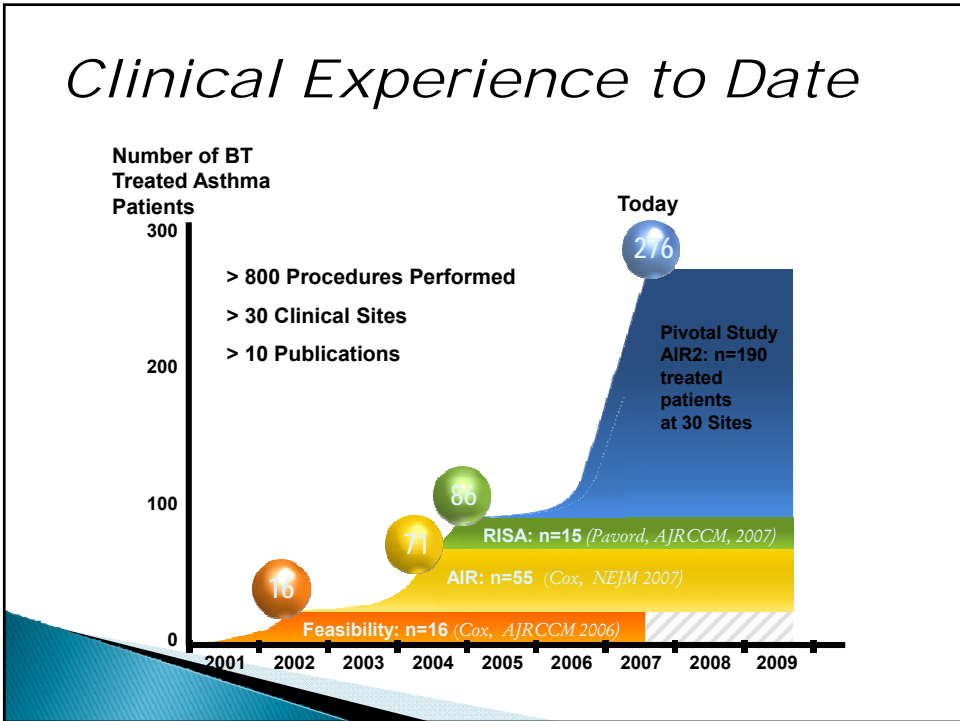
## ***The Alair<sup>®</sup> System***

- ▶ The Alair Catheter is a flexible tube with an expandable wire array at the tip
- ▶ The Alair Radiofrequency Controller supplies energy via the Catheter to heat the airway wall

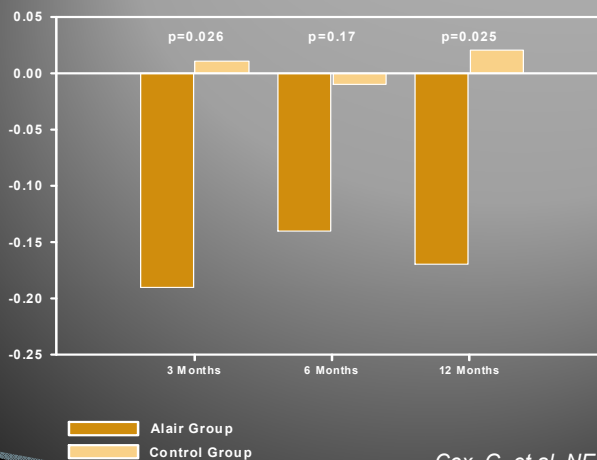


# Bronchial Thermoplasty Clinical Program

» The evidence



## AIR Trial: Demonstrated Reduction in Mild Exacerbations



Cox, G. et al. NEJM, 2007

## RISA Trial: Demonstrated Decrease in Oral Steroid Usage

- ▶ Subjects Completely Weaned Off Oral Corticosteroids:
  - 4/8 Subjects in Alair group
  - 1/7 Subjects in Control group
- ▶ Reduction in Oral Corticosteroid Use:

	BT Group (N)	Control Group (N)	P-value
Percent Reduction in OCS	63.5 ± 45.4 (8)	26.2 ± 40.7 (7)	0.12

Pavord, ID, et. al. AJRCCM, 2007

## **Long-Term Safety**

- ▶ 3 year follow-up in Feasibility, AIR & RISA trials:
  - Stable pulmonary function
  - No clinical complications based on AE reporting
- ▶ Annual CT scans for 5 years (Feasibility Study):
  - All patients doing well
  - No clinically significant findings
- ▶ Alair treatment has excellent safety profile long-term

Castro et al. Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma: A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial  
Am. J. Respir. Crit. Care Med. 2009

## **AIR2 Trial**

- ▶ Purpose: Pivotal US IDE Study
  - For FDA approval for use in asthma
- ▶ Study Population:
  - Severe Persistent Asthma
  - Symptomatic despite High dose ICS + LABA
- ▶ Primary Endpoint: Asthma Quality of Life Questionnaire (AQLQ)

## ***AIR2 Trial Design***

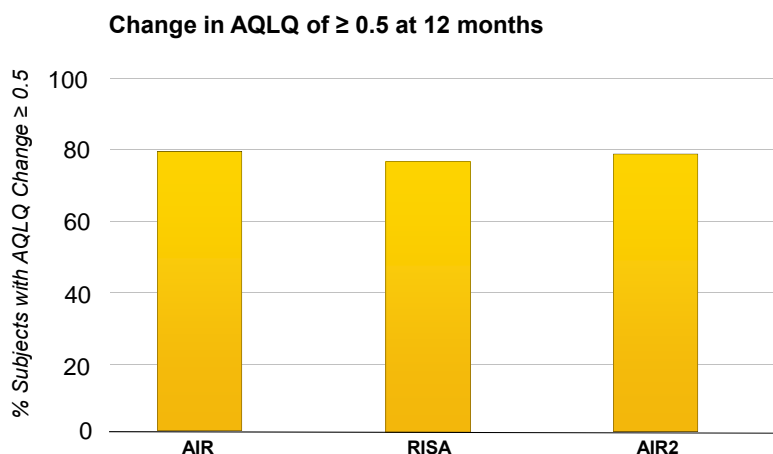
- ▶ Study Design: Sham Controlled, Double Blind
  - 2 : 1 randomization; BT: Sham
  - BT Group (ICS + LABA + BT)
  - Sham Group (ICS + LABA + Sham)
- ▶ Study Size: 297 Subjects / 30 centers (International)
- ▶ Length of Follow-up:
  - One year
  - 5-year safety follow-up for BT subjects

## ***AIR2: Demonstration of Improvement in Quality of Life***

- ▶ Met primary endpoint – Change in AQLQ\*
  - 79% of treated patients achieve  $\geq 0.5$  increase\*
  - Effect persistent across 6, 9, and 12 months\*

Castro et al. **Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma: A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial**  
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## Consistency in % Responders Across Studies



## Clinical Benefits of BT

- ▶ 32% reduction\* in the rate of severe exacerbations
- ▶ 66% reduction\* in the number of days lost from work, school or other activities
- ▶ 84% reduction\* in ER visits
- ▶ 73% reduction in hospitalizations
- ▶ 23% reduction in unscheduled physician office visits

Castro et al. Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma: A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial  
Am. J. Respir. Crit. Care Med. 2009

\* Statistically significant

## ***AIR2 Trial Safety***

- ▶ 850 bronchoscopies in Subjects with Severe asthma (558 BT and 292 Sham)
- ▶ No incidences of:
  - Pneumothorax
  - Intubation
  - Mechanical ventilation
  - Airway stenosis or focal narrowing
  - Cardiac arrhythmias
  - Death

## ***Treatment Period Hospitalizations for Respiratory Symptoms***

<b>Alair (N=190)</b>		<b>Sham (N=98)</b>	
<b>19 Hospitalizations in 16 Subjects</b>		<b>2 Hospitalizations in 2 Subjects</b>	
<b>No. of Events (Incident Rate %)</b>		<b>No. of Events (Incident Rate %)</b>	
Asthma Aggravated	12 (6.3%)	Asthma Aggravated	2 (2.0%)
Atelectasis	3 (1.6%)		
Lower Resp. Tract Infect.	1 (0.5%)		
Hemoptysis	1 (0.5%)		
Low FEV <sub>1</sub>	1 (0.5%)		
Aspirated tooth in airway	1 (0.5%)		

### ***Risk of Respiratory-Related Hospitalization Following Procedure***

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

\* 10/17 (59%) in the Alair group occurred on the day of the procedure.

### ***Clinical Summary of Bronchial Thermoplasty***

- ▶ Despite a transient worsening of asthma
  - Typically occurring within one day and resolving within one week with standard care
- ▶ Patients experience long term benefits out to at least one year:
  - Improvement in quality of life
  - Decrease in severe exacerbations
  - Decrease in ER visits
  - Decrease in days lost from work or school

## Demonstration of Effectiveness Across Multiple Studies

<b>AIR2</b> (RCT; n = 288)	<b>AIR</b> (RCT; n = 109)	<b>RISA</b> (RCT; n = 32)
<ul style="list-style-type: none"> <li>▶ AQLQ</li> <li>▶ Exacerbations</li> <li>▶ ER visits</li> <li>▶ Days missed work/school</li> </ul>	<ul style="list-style-type: none"> <li>AQLQ</li> <li>Exacerbations</li> <li>Rescue meds</li> <li>Symptom Free Days</li> </ul>	<ul style="list-style-type: none"> <li>AQLQ</li> <li>ACQ</li> <li>Rescue meds</li> <li>Oral Steroids (p = 0.12)</li> </ul>
<p>ATS, May 2009</p>	<p>NEJM, v356, Mar 2007</p>	<p>AJRCCM, v176, Sep 2007</p>
<p>All of the above were shown to be significant (p &lt; 0.05), except where noted.</p>		

## Who is Appropriate for Bronchial Thermoplasty?

- ▶ Adult asthmatics
- ▶ Inadequate control despite combination of high dose inhaled corticosteroids (ICS) and a long-acting  $\beta_2$ -agonist (LABA)
- ▶ Able to undergo bronchoscopy per hospital guidelines

## ***Who Will Perform Bronchial Thermoplasty?***

- ▶ Pulmonologists who have demonstrated an expertise in bronchoscopy
- ▶ Centers of excellence throughout the country
- ▶ Training will be required by manufacturer
  - Didactic technical review
  - Bronchial thermoplasty computer-based simulator learning module
  - Model-based hands-on technical team training

## ***Summary: New technology for managing asthma***

- ▶ Asthma management continues to be the subject of multiple investigations.
- ▶ Current treatment guidelines are adequate for most asthmatics, but there are still many unmet clinical needs.
- ▶ Sub-varieties of asthma such as eosinophilic asthma and neutrophilic mediated asthma are being studied closely to identify potential new pharmacotherapies
- ▶ Bronchial thermoplasty represents a new and unique minimally invasive technology targeted at smooth muscle hyperplasia in selected asthmatics.
- ▶ New and emerging therapeutic modalities will continue to be needed to meet the challenges of this disease.