THE PROMISE OF NEW AND NOVEL DRUGS

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Asthma Prevalence, Morbidity, Mortality

- 235 million suffer from asthma worldwide
- Prevalence among adults (>15 years) is rising from 2.3% in 1979 to 8.4% in 2004.
- Estimated number of people suffering from asthma will grow by 100 million by 2025
- Worldwide deaths >250,000/year
Asthma Prevalence, Morbidity, Mortality in USA

- 24.6 million People diagnosed with asthma
- 12.8 million People experience asthma attacks
- 1.8 million Emergency room visits
- 456,000 Hospitalizations
- 3,447 Asthma-related deaths

Approximately 9 People Die From Asthma/Day

Annual incidence, based on 2007 data
Burden of Asthma

- Health care expenditures very high
- Developed economies might expect to spend 1-2 percent of total health care expenditures on asthma. Developing economies likely to face increased demand
- Poorly controlled asthma is expensive; investment in prevention medication likely to yield cost savings in emergency care
What is asthma?

A *chronic inflammatory disorder of the airways* in which many cells play a role: mast cells, eosinophils and T lymphocytes.

In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough at night and/or in early morning.

Inflammation also causes an *associated increase in airway responsiveness* to a variety of stimuli.

Risk Factors that Lead to Asthma Development

**Host Factors**
- Genetic predisposition
- Atopy
- Airway hyper-responsiveness
- Gender
- Race/Ethnicity

**Environmental Factors**
- Indoor allergens
- Outdoor allergens
- Occupational sensitizers
- Tobacco smoke
- Air Pollution
- Respiratory Infections
- Parasitic infections
- Socioeconomic factors
- Family size
- Diet and drugs
- Obesity
Mechanisms Underlying the Definition of Asthma

Risk Factors (for development of asthma)

- Inflammation
- Airway
- Hyperresponsiveness
  - Risk Factors (for exacerbations)
  - Airflow Obstruction
    - Symptoms
Airway inflammation

- Airway Hyper responsiveness
- Airway obstruction
- Airway remodeling: basement membrane thickening, collagen deposition, goblet cell hyperplasia, mucus, SM hypertrophy (irreversible airway narrowing, persistent airflow obstruction)
Ideal route is inhaled: rapid delivery to the lungs with minimal systemic effects
Airway hyper-responsiveness and obstruction can be temporarily be reversed by drugs, prevention of airway remodelling and SM hypertrophy can be challenging
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Low-dose ICS + LABA
OR
Medium-dose ICS
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 3
Preferred: Medium-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 4
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 6
Step up if needed
(first, check adherence, environmental control, and comorbid conditions)

Assess control
Step down if possible
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Sequelae of poorly controlled asthma

- Recurrent Hospitalizations
- Severe and fixed airflow obstruction
- Severe asthma exacerbations
**Impact of Asthma Severity**

**Cost/Patient/Year**

- **Mild**: $2,200
- **Moderate**: $4,800
- **Severe**: $12,800

**Est. $20.7B annual healthcare costs**

## World Health Organization (WHO) definition of severe asthma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Proposed management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated severe asthma</td>
<td>Address healthcare and medication access</td>
</tr>
<tr>
<td>Difficult-to-treat severe asthma</td>
<td>Address non-adherence</td>
</tr>
<tr>
<td></td>
<td>Ensure correct device usage</td>
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<tr>
<td></td>
<td>Smoking cessation</td>
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<tr>
<td></td>
<td><strong>Avoidance of triggers</strong></td>
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<tr>
<td></td>
<td>- occupational/ environmental allergens,</td>
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<td></td>
<td>- medications like non-selective beta-blockers, aspirin, ACE inhibitors.</td>
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<tr>
<td></td>
<td><strong>Manage comorbidities</strong></td>
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<tr>
<td></td>
<td>- Rhinosinusitis: CT scan, nasoendoscopy</td>
</tr>
<tr>
<td></td>
<td>- Gastric reflux: 3 months of empirical proton pump inhibitors/ esophageal pH testing</td>
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<tr>
<td></td>
<td>- Obesity: weight control</td>
</tr>
<tr>
<td></td>
<td>- Obstructive sleep apnea: polysomnography</td>
</tr>
<tr>
<td></td>
<td>- Depression, anxiety: psychiatrist evaluation</td>
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</table>

## Treatment-resistant severe asthma

- **a.** Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma

- **b.** Asthma for which control can be maintained only with the highest level of recommended treatment and are at risk of treatment adverse effects.

<table>
<thead>
<tr>
<th>Proposed management</th>
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</thead>
<tbody>
<tr>
<td>Novel therapies</td>
</tr>
<tr>
<td>- immunotherapy</td>
</tr>
<tr>
<td>- bronchial thermoplasty</td>
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<tr>
<td>Close monitoring avoid premature stepping down of medications</td>
</tr>
</tbody>
</table>
Definition of severe refractory asthma

for patients with asthma in whom alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been checked, but still have poor asthma control or frequent (>2) severe exacerbations per year despite the prescription of high-intensity treatment or can only maintain adequate control when taking systemic corticosteroids and are thereby at risk of serious adverse effects of treatment.
Severe Refractory Asthma

Prevalence (NAEPP) = 5-10%, Symptomatic (4 out of 10).

- Medications are limited, require adherence, have serious side effects
- High economic costs and resource utilization a/w medications, hospitalizations, physician visits and lost days of work/school ~ $20.7B
- Additional therapeutic treatment options are needed

**Major characteristics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (µg/day)</th>
<th>Dose (puffs/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Beclomethasone dipropionate</td>
<td>&gt;1260</td>
<td>&gt;40 puffs (42 µg/inhalation)</td>
</tr>
<tr>
<td>b. Budesonide</td>
<td>&gt;1200</td>
<td>&gt;20 puffs (84 µg/inhalation)</td>
</tr>
<tr>
<td>c. Flunisolide</td>
<td>&gt;2000</td>
<td>&gt;6 puffs</td>
</tr>
<tr>
<td>d. Fluticasone propionate</td>
<td>&gt;880</td>
<td>&gt;8 puffs</td>
</tr>
<tr>
<td>e. Triamcinolone acetonide</td>
<td>&gt;2000</td>
<td>8 puffs (110 µg), &gt;4 puffs (220 µg)</td>
</tr>
</tbody>
</table>

**Minor characteristics**

1. Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, e.g. long-acting agonist, theophylline, or leukotriene antagonist
2. Asthma symptoms requiring short-acting agonist use on a daily or near daily basis
3. Persistent airway obstruction (FEV1 < 80% predicted; diurnal PEF variability > 20%)
4. One or more urgent care visits for asthma per year
5. Three or more oral steroid ‘bursts’ per year
6. Prompt deterioration with 25% reduction in oral or inhaled corticosteroid dose
7. Near fatal asthma event in the past

In order to achieve control to a level of mild-moderate persistent asthma: (1) treatment with continuous or near continuous (50% of year) oral corticosteroids; (2) requirement for treatment with high-dose inhaled corticosteroids. Reproduced with permission [41].

*Definition of refractory asthma requires one or both major criteria and two minor criteria
Suboptimal Tx based on Phenotypes: atopic, intrinsic/nonatopic, extrinsic
Endotyping of underlying molecular mechanisms: antiIL5 in persistent
eosinophil expression; antiIL13 for high periostin stimulated by IL13
Approaches to improve outcome

- **Optimizing bronchodilation:** Tiotropium

  Compare Tiotropium vs LABA vs doubling ICS. Tiotropium, salmeterol better than doubling ICS in improving PEF, FEV1 and control. Tiotropium > LABA in evening PEF, prebronchodilator FEV1. *Peters SP* NEJM 2010

  Adding Tiotropium to combination therapy: improved FEV1

- **Reducing airway smooth muscle:** Bronchial Thermoplasty
Bronchial Thermoplasty Clinical Studies

- Over 800 Procedures Performed
- 3 Randomized Controlled Studies
- Over 10 Publications

Pivotal Study
AIR2: n=190 treated patients at 30 sites
(Castro, AJRCCM, 2010) ¹
(Castro, AAAI, 2011) ⁵

AIR: n=55
(Pavord, AJRCCM, 2007) ²
(Cox, NEJM, 2007) ³

RISA: n=15
(Cox, AJRCCM, 2006) ⁴

Feasibility: n=16

AIR = Asthma Intervention Research Study
AIR2 = Asthma Intervention Research 2 Study
RISA = Research in Severe Asthma Study
AIR2 - Pivotal Clinical Trial

- Sham controlled, double blinded
  - Severe persistent asthma (297 patients)
  - Symptomatic despite high dose ICS + LABA

- Primary Endpoint: Asthma Quality of Life Questionnaire score

- Follow-up: One year, 5-year safety follow-up for BT subjects

- Improved AQLQ score at 1 yr:
  79% treated patients achieved ≥ 0.5 increase, persistent 6, 9, 12 mths

- Improved clinical outcomes at 1 yr:
  32% decrease in severe exacerbations
  84% reduction in ER visits for respiratory symptoms
  73% reduction in hospitalization for respiratory symptoms
  66% less days lost from work, school and other daily activities

- No device-related adverse events or deaths, Acceptable safety profile

Persistence of Effect at Two Years

- Reduction in severe exacerbations at years 1, 2

Long-Term Safety Profile

- Safety data: 2/5 years (85% patients underwent BT AIR2):
  - No deaths in the BT group
  - Absence of long-term clinical complications (AE reporting)
  - Stable pulmonary function: pre-/post-bronchodilator FEV$_1$ yr 1-5 yrs. CT scans at 2, 5 years (85% BT patients) no clinically significant structural changes

- Sustained reduction in asthma attacks and ER visits

Journal of Allergy and Clinical Immunology

Unlike current available therapies with short-term effect, single BT treatment (3 procedures) provides long-term benefit that may lead to long-term savings (sustained reduction in asthma attacks and ER visits)
## Procedure Safety

6 weeks after the last bronchoscopy procedure to 12 month follow-up

- 850 bronchoscopies (558 BT and 292 Sham procedures)
- More respiratory adverse events reported in BT grp occurring within one day and resolving within 1/52 of BT
- Fewer respiratory adverse events, hospitalizations, ER visits in BT grp during post-treatment period

### Respiratory-Related Hospitalizations during Treatment Period

<table>
<thead>
<tr>
<th></th>
<th>BT (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events / Subject (%)</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.

*Castro, Am J Respir Crit Care Med. 2010;181(2):116-24*
What contributes to asthma severity?

Severe asthma

60%

Persistent eosinophilic bronchitis

HES
Vasculitis
CEP
Chronic Rhino Sinusitis-non atopic

30%

Persistent Neutrophilic bronchitis

Infection

10%

Persistent Airway Hyper responsiveness

smooth muscle ?mast cell
? Mediators
? T-cell
Approaches to improve outcome

- Reduce airway inflammation: 50% severe asthma exacerbations are eosinophilic, remaining neutrophilic
- Sputum induction to guide tx: Hamilton strategy
# Sputum cell counts in healthy adults

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Mean</th>
<th>2SD</th>
<th>Median</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCC $10^6$ /g</td>
<td>4.1</td>
<td>13.8</td>
<td>2.4</td>
<td>9.7</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0.4</td>
<td>2.2</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>37.5</td>
<td>77.7</td>
<td>36.7</td>
<td>64.4</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>58.8</td>
<td>100</td>
<td>60.8</td>
<td>86.1</td>
</tr>
</tbody>
</table>

*Am J Respir Crit Care Med 2000; 161: 475-8*
Reduce eosinophils: oral steroids, anti IL 5 monoclonal antibody (Mepolizumab)

- Decrease blood and airway eosinophils, reduction of OCS (withdrawal), less exacerbations, better control, improve FEV1. Nair P. NEJM 2009.

- **Antisense** to reduce mRNA for translation into proteins needed to produce cytokine receptors that mediate effects of cytokines for eosinophil maturation, survival and migration. Studies on antisense against receptors for IL5,3, GMCSF, chemokine receptor CCR3 (for eotaxin). Result: reduce allergen induced airway eosinophilia in mild asthmatics in dose-dependent fashion

- Th2 lymphocytes have receptor on cell surface activated by prostaglandin D2: CRTh2. CRTh2 antagonists for pts with persisting asthma not on regular ICS: improved FEV1, QOL, night-time symptoms, sputum E count.
- **Reduce neutrophils:** IL8, mediated by chemokine receptor CXCR2. Antagonist to CXCR2 and demonstrated to prevent ozone-induced airway neutrophilia in normal subjects, also promise in severe asthma with airway neutrophilia *Gaga M. AJRCCM 2010*

- **Targeting specific airway effector mediators**
Strategies to decrease 'steroid resistance'

Barnes PJ, Lancet 2009
Asthma not a single disease
1 size fits all treatment approach faces major challenges
Personalized medicine
Drugs

**Anticholinergic bronchodilators:** cholinergic mechanisms in late response to inhaled allergen. Epithelial and inflammatory cells release acetylcholine. Tiotropium: inhibits eosinophilic inflammation, mucin gene expression and airway remodelling

**AntiIgE (Omalizumab):** monoclonal Ab binds to Fc portion of IgE – mast cells, basophils and dendritic cells. Reduces exacerbations, improved symptoms and QoL.

**Leukotriene inhibitor** LTB4 chemoattractant of neutrophils, mast/ T cells.

**PDE4 inhibitors** – T cells, eosinophils, neutrophils, mast cells, airway SM, epithelial cells and nerves. Roflumilast (COPD)

**HDAC2 activation:** low dose theophylline, nortriptyline

**Macrolides:** mycoplasma/chlamydia/neutrophilic asthma

**Cytokine/ chemokine blockade,** Kinase/ mast cell inhibitors

**Steroid resistance phenotype:** p38 MAPK inhibitors; MIF (-)
Bronchial Thermoplasty - Reduces ASM

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

- Outpatient bronchoscopic procedure:
  - Delivers controlled energy to airways of lungs
  - Reduces excess airway smooth muscle, decreases bronchoconstrictions/exacerbations
  - For treatment of severe refractory asthma not well controlled on ICS and LABA

- Demonstrated to increase asthma control and improve asthma-related quality of life in patients with severe asthma

- Complementary treatment: not a cure or replacement for current asthma medications
Reduced Airway Smooth Muscle

- 3 years post-treatment (canine model)

Masson’s Trichrome stain
Airway Responsiveness to Methacholine Challenge

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

Bronchial Thermoplasty Patient Selection

Alair® Bronchial Thermoplasty System: FDA approved

Indications:

- Adult severe, persistent asthmatics (≥ 18 years old)
- Inadequate control despite combination of inhaled high dose corticosteroids (ICS) and a long-acting beta₂-agonists (LABA)
- Able to safely undergo bronchoscopy per hospital guidelines

Contraindications

- pacemaker, internal defibrillator, implantable electronic device
- known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines
- previously been treated with the Alair® System
Bronchial thermoplasty should be delayed if:

- Active respiratory infection
- Asthma attack in past 2 weeks
- Known bleeding disorder
- Patient is unable to stop taking anticoagulants, antiplatelet agents, aspirin before the procedure

Pre-procedural Evaluation

- Pre-procedure post bronchodilator FEV1 85% baseline
- OCS 3 days prior day of and day after procedure
- Albuterol nebulizer, moderate sedation, glycopyrrolate
- RF energy delivered to airways ~60 activations/ procedure
- Patient monitored 2–4 hours post-op and discharged home if on stable within 80% of pre-procedure post Bronchodilator FEV$_1$
Alair® Bronchial Thermoplasty System

- **Alair Catheter** - a flexible tube with an expandable wire array (introduced into the lungs via bronchoscope)

- **Alair Radiofrequency (RF) Controller** - supplies energy via Catheter to the airway wall

Temperature controlled energy (650°C) delivered to airway wall for 10 seconds per activation - no permanent damage to epithelium

4 activations in a sub-segment
Three Treatment Sessions

Bronchial thermoplasty is performed in 3 separate treatment sessions each scheduled approximately 3 weeks apart.
33 yr monk asthma for 15 yrs, on oral steroids 10mg OM for 10 yrs, with monthly increase to 30mg for 1 week. Ventolin puffs 12/day and nebulizations 3X/day. Hospitalizations 1-2/yr when above measures fail, not intubated.

- Triggers incense burning, pollution, smoke—challenging pt as it is vocation, personal choice/calling
- Needs to take frequent breaks from chanting
- Compliant on symbicort 4 puffs bd, theophylline, singulair
- ACT 5-6, consulted for BT cannot afford antiIG E.
- Bronchoscopy: diffuse bronchospasm minimal secretions
- After 1 BT, easier to breathe R lower lung, after BT2, ACT score increased 15, after BT3 ACT 21.
- PEFR 250l/min- 680 l/min after BT3, Can chant longer, less chest tightness, uses 1 ventolin puff/day before sleep, no nocturnal awakenings
- “Can breathe better, no chest tightness only cough but prefers cough over chest tightness anytime”