Asthma 2013: Clinical Highlights and Controversies

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Trends of Asthma Morbidity/ Mortality

Asthma Facts: Each Day
- 44,000 asthma attacks
- 4,700 visit E.D. with asthma
- 1,200 admitted to a hospital
- 9 people die from asthma

Racial Disparity in U.S.

Asthma: more common in developed countries
Exacerbations more common in:
- Minority populations
- Lower socio-economic groups

Prevalence of asthma

- Hispanic: 8.1%
- White: 5.9%
- Black: 8.8%

DATA SOURCE: CDC/NCHS, National Health Interview Survey, January–March 2013, combined Sample Adult and Sample Child Core components.
Time to be optimistic?

National Health Interview Survey (NHIS)

- Prevalence of current asthma increased:
  2003 vs. 2012 = 7.1% vs. 8.5%
- Percentage with exacerbation fell 8.5% to 6.8%

Still 3,285 unnecessary asthma deaths!
Asthma is a Complex Disease

- Genetics of asthma
  - One parent: risk 1/3
  - Both parents: risk 7/10
  - Identical twin: only 50-70%

- Environment & asthma
  - Increased risk: western lifestyles, use of antibiotics and vaccines, allergen exposure
  - Decreased risk: large number of siblings, rural environment

- Timing: early vs. late exposure (e.g. cats, infection)
Evolution of Asthma Paradigms

1970s–1980s
Bronchoconstriction (Spirometry)

1980s–1990s
Inflammation (PC_{20}, Inflam cells, FeNO)

1990s–2000s
Remodeling

Symptoms
Relieve Symptoms
Prevent Symptoms
Prevent Attacks
Prevent Remodeling

Fixed Obstruction
Prevent Symptoms
Prevent Attacks
Prevent Remodeling

Bronchial Hyperreactivity
The Airway Microenvironment in Asthma

- Basophil
- Mast cell
- Eosinophil
- IgE
- Th2-cell
- IL-4, IL-13
- GM-CSF
- IL-9
- IL-4
- IL-5
- IL-13

Structural Impairment
- Fibroblasts
- VEGF
- ET-1
- TGFβ
- Blood vessel
- Smooth muscle

Inflammation
- Nerves

Mucus
- Eotaxin

Dendritic cell

IL-4, IL-13

IgE
Basement Membrane Thickening

Changes in Lung Function in Asthma

Martinez F, Vercelli D. Lancet 2013
Clinical Asthma Phenotypes

Asthma Phenotypes

• Early onset asthma: ≤ 12 yrs old
  – Atopic (elevated IgE levels): skin, nasal, & lung involvement
  – Eosinophilic inflammation; allergy driven/responsive

• Adult onset asthma: > 18 yrs old (mean 54; range 26-75)
  - Group 1: Eos +; persistent airflow obstruction; low Sx score
  - Group 2: Obese females, low Eos, high Sx score/health costs
  - Group 3: Mild-moderate asthma, nl lung function and low inflammatory markers

• Severe asthma phenotype
  – Disease moves more distal in airways
  – Neutrophils and mast cells in terminal airways

Allergy 68 (5), 674-80 (May 2013)
Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes and each having a specific biological mechanism

<table>
<thead>
<tr>
<th>Endotype 1</th>
<th>Endotype 2</th>
<th>Endotype 3</th>
<th>Endotype 4</th>
<th>Endotypes not yet identified or rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen driven</td>
<td>Severe eosinophilic non-allergic</td>
<td>Non-eosinophilic</td>
<td>Non-inflammatory</td>
<td></td>
</tr>
</tbody>
</table>

The Asthma Syndrome
Symptoms of asthma, episodic breathlessness, wheeze, cough

Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome

Jan Lötvall, MD, a Cezmi A. Akdis, MD, b Leonard B. Bacharier, MD, c Leif Bjermer, MD, d Thomas B. Casale, MD, e Adnan Custovic, MD, f Robert F. Lemanske, Jr, MD, g Andrew J. Wardlaw, MD, h Sally E. Wenzel, MD, i and Paul A. Greenberger, MD j

Göteborg and Lund, Sweden, Davos, Switzerland, St Louis, Mo, Omaha, Neb, Manchester and Leicester, United Kingdom, Madison, Wis, Pittsburgh, Pa, and Chicago, Ill
#1 Cause of Asthma Deaths

- **Noncompliance**
  - Lack of asthma education (both patients/MDs)
  - Failure to prescribe/use controller medications
- **Belief that asthma deaths only occur in patients with severe asthma**

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**Pediatric Asthma Deaths: Mild Patients Are Also at Risk**

Findings from a cohort study reviewing all pediatric asthma-related deaths (n=51) in the Australian state of Victoria from 1986 to 1989.

Patient Education/Beliefs Can Prevent Asthma Deaths

Patient-related Factors: Belief in Treatment Efficacy Is Associated With Higher Adherence

- High adherence
- Low adherence

![Graph showing percentage of respondents regarding treatment efficacy.

Low-dose ICS: Prevention of Death from Asthma

Education About the Environment

• Allergens avoidance in asthma:
  – House dust mite
  – Cat dander
  – Cockroach antigen
  – Alternaria/fungi

• Most forgotten component in asthma education
Smoking Cessation/Eliminate ETS

- Over 20% of asthmatics smoke
- Cigarette smoke:
  - Increases mucous production
  - Causes destruction of cilia
  - Induces bronchospasm
- ETS has been shown to be equally detrimental as smoking
- Induces resistance to steroids

Eur Respir J 2009; 33:1010–1017
Risk Factors for Severe Asthma Exacerbation

- Equal among mild, moderate, and severe asthma*
- Key risk factors:
  - Ever been intubated or in ICU for asthma
  - Hospitalized in last year
  - Deficiency in self-management skills
- Predictors of health care utilization:
  - Score of < 20 on Asthma Control Test (ACT)
  - Poor perception of dyspnea

* Clin & Exper Allergy 2007; 37:552-557
Factors Influencing the Heterogeneity of Asthma Control: Poor Perception of Dyspnea (POD)

113 Asthmatics Evaluated

- Breathe against 2-way valve load of 0-, 5-, 10-, 20-, and 30-cm H$_2$O for 1 minute
- Dyspnea defined as modified Borg scale
- POD
  - Low  29 (26%)
  - Normal  67 (59%)
  - High   17 (15%)

- $\beta_2$-Agonist use in 4 weeks*
  - Low   1.7/day
  - Normal 2.4/day
  - High  4.1/day

- Patients with asthma and a low POD had tendency toward
  - Older age
  - More females
  - Longer duration
  - More severe

- Documented events over 2 years

*Puffs/day.
Poor Perception of Dyspnea (POD)

- ED Visits: 32 (Low POD 8, Normal POD 14, High POD 14)
- Hospitalizations: 22 (Low POD 4, Normal POD 3, High POD 15)
- Near-Fatal Asthma: 13 (Low POD 2, Normal POD 1, High POD 10)
- Death*: 6 (Low POD 1, Normal POD 1, High POD 4)

*Of deaths in the low POD group, 4 were asthma related, 2 were unknown.

Multiple studies now that show underpercievers and life-threatening asthma may have a 20% mortality from asthma.
Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school, or at home?

2. During the past 4 weeks, how often have you had shortness of breath?

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

5. How would you rate your asthma control during the past 4 weeks?

Well controlled ≥ 20; 16-19 not well controlled, ≤ 15 very poorly controlled
Available at: http://www.asthmacontrol.com.

• ACT < 20 best predictor of asthma control
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• Maximizing therapy
• Controversies in asthma care
What is Persistent Asthma?

- Use of rescue inhaler each week
- Nocturnal awakenings/ month
- Number of canisters per year of rescue medications
  - More reliable index
  - Two puffs 3x/week = 3.3 canisters/year
NAEPP Guidelines to the Management of Asthma

**Figure 4-5. Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults**

**Intermittent Asthma**

**Persistent Asthma: Daily Medication**
- Consult with asthma specialist if step 4 care or higher is required.
- Consider consultation at step 3.

**Step 1**
- Preferred: SABA PRN

**Step 2**
- Preferred: Low-dose ICS
- Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 3**
- Preferred: Medium-dose ICS + LABA OR Medium-dose ICS + LTRA OR Medium-dose ICS + Theophylline OR Zileuton
- Alternative: Low-dose ICS + LABA AND Low-dose ICS + LTRA AND Low-dose ICS + Theophylline AND Low-dose ICS + Zileuton

**Step 4**
- Preferred: High-dose ICS + LABA AND Consider Omalizumab for patients who have allergies
- Alternative: High-dose ICS + LABA AND High-dose ICS + LTRA AND High-dose ICS + Theophylline AND High-dose ICS + Zileuton

**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.
Can Guideline-defined Asthma Control Be Achieved?

- **GOAL Study**: Double blind RCT
  - Steroid naive or “low” dose ICS
  - Age 12-80 (n = 3421)
- Total control =31%
- Well controlled = 59-71%
- Prednisone .5 mg/kg x10 days improved control by 5-10%
- Exacerbation rate ≈ 10%
- Conclusion: 20% not well controlled on steroids/LABA

*Am J Respir Crit Care Med 2004, 170 (8): 836–44*
Theophylline

Rationale:

- Long-acting bronchodilator by non-selective inhibition of phosphodiesterases
- Anti-inflammatory effects:
  - ↓ Infiltration of lymphocytes and eosinophils into the airway
  - ↓ T-cell proliferative response cytokine production.
  - ↑ Apoptosis of eosinophils

Theophylline

- ICS vs. theophylline + ICS vs. theophylline alone. In asthmatic smokers.
- The combination of theophylline + ICS provided the best results improving ACQ scores and pulmonary function.

Nie H, et al. Resp Med. 2013 (n = 325)
- ICS/LABA + theophylline vs. ICS/LABA + placebo in a randomized, parallel-group study (24 weeks)
- Patients receiving theophylline had fewer exacerbations (≥ 1) 30 vs. 47 % (p = 0.004).
- Theophylline group had significant decreased in sputum eosinophils and eosinophilic cationic protein.
Theophylline

Pros:

- Modest bronchodilation
- Possible anti inflammatory effects
- Possible reversal of steroid resistance
- Convenient dosing
- Potentially more beneficial in asthmatic smokers

Cons:

- Need to monitor levels
- Potentially severe side effects
- Interaction with other medications
- Limited evidence of effectiveness
Long acting muscarinic antagonists

✓ Rationale:

- Activation of the parasympathetic (acetylcholine) system causes bronchoconstriction, bronchial vasodilation and mucus secretion. Asthma may cause increased parasympathetic afferent stimulation.

✓ Approved for COPD:

- Tiotropium: reduces smooth muscle contraction and mucus secretion.

- Aclidinium: newly approved. Few data on asthma.
Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

- **TALC study**
  - Poorly controlled on ICS
    - Double ICS
    - LABA (salmeterol)
    - LAMA (Tio)

- **Primary endpoints**
  - PEFR
  - FEV\(_1\)
  - Asthma control days

- **LAMA = LABA > ↑ ICS**

- No long term data; select subset of subjects

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October 28, 2010
Long acting muscarinic antagonists

• Kerstjens et al. J Allergy Clin Immunol. 2011 \( (n = 107) \)
  – Tiotropium as an add-on to ICS + LABA.
  – Poorly controlled, severe asthma: tiotropium improved FEV\(_1\) over 24 hrs

• Kerstjens et al. \((n = 912)\)
  – Increased time to first exacerbation by 56 days
  – 21% reduction in the risk of a severe exacerbation\(^*\)

\(^*\) Note: “Severe” = Double ICS x 3 days
FEV1 increased 88 +/- 31 ml

NEJM 2012;1198-1207

Is this clinically meaningful?
Omalizumab: Indications

- Patients with allergic asthma ages 12 years & older (6 years old: Europe)
- Step 5-6 NAEPP Guidelines -2007
- IgE level: 30-700 IU/ml
- One positive perennial antigen by skin test or RAST/Immunocap
Omalizumab

Evidence:

– Multiple studies have shown efficacy in:
  - Quality of life
  - Exacerbations
  - ER visits
  - Hospitalizations
  - Steroid requirements

Omalizumab in patients with IgE levels of 30-700 vs. above 700 IU/ml (n = 52)

Omalizumab

**Pros:**
- Clear evidence of ↓ of exacerbations, ER visits, hospitalization & oral steroid requirements

**Cons:**
- High cost
- Frequent visits required (every 2-4 weeks)
- Subcutaneous dosing
- Not clear when to stop therapy
- Possibly limited therapeutic window
ASTHMA 2013

- Maximizing therapy
- Controversies in asthma care
Measurement of Nitric Oxide?

ATS Guidelines

• $< 25 \text{ ppb (} 20 \text{ ppb in children)}$ - eosinophilic inflammation and responsiveness to corticosteroids are less likely

• $>50 \text{ ppb (}> 35 \text{ ppb in children)}$ eosinophilic inflammation and responsiveness to corticosteroids in sx patients is more likely

• $25-50 \text{ ppb (} 20–35 \text{ ppb in children)}$ depends on the clinical context
Reasons to Measure Nitric Oxide

- Identify the eosinophilic asthma phenotype
- Assess potential response or failure to ICS
- Assist in the evaluation of adherence to anti-inflammatory medications
- Guide changes in doses of anti-inflammatory medications

Studies have not been able to show FENO impacts lung function, QOL, or rate of asthma exacerbations but increased ICS use

Use of FENO in Management of Asthma: Pro

- **Initial studies:**
  - Often mild asthma
  - Small numbers
  - Evaluated number of pts with exacerbations

- **Donahue analysis**
  - Evaluated total number of exacerbations

Reanalysis of Cochrane Studies

Ongoing study: using FENO to titrate ICS

Respir Med 2013;10(7):943-52
Bronchial thermoplasty (BT)

Rational or Irrational?

- Asthma: characterized by airway remodeling with smooth airway smooth muscle (ASM) hyperplasia/hypertrophy
- BT: can decrease significantly the ASM mass (via radiofrequency energy/ablation)
Bronchial thermoplasty

Airway of Person with Severe Asthma
- More airway muscle causes airway to narrow

This is the area where Alair applies heat to the airway wall during BT treatment

Airway of Person with Severe Asthma after Treatment
- Reduced airway muscle after BT treatment
- After BT, the inside airway wall and other tissue heals, but airway muscle is reduced
Bronchial thermoplasty

- **Pros:**
  - Some evidence of reduction of symptoms
  - Apparent lasting effects (≥ 5 years)

- **Cons:**
  - High cost
  - Early exacerbation rate despite pre-treatment with oral steroids
  - Need for 3 bronchoscopies
Can Asthma Be Prevented?

- **Concept:** Maternal and epigenetic factors (how environment changes gene activity) are key factors in the development of allergy and asthma.

- **Current recommendations:**
  - Breast feed and avoid cow’s milk first 4-6 months.
  - Use hydrolyzed formula if breast feeding not possible.
  - Avoid ETS during pregnancy and lactation.

- **Controversial data:**
  - Change infants microbiome (probiotics).
  - Early introduction of peanuts & hen’s eggs.
  - Early antigen avoidance (Isle of Wright Study).
Questions?