

## Asthma 2011 Currents Concepts in Pathogenesis and Treatment

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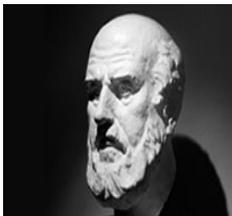
## Asthma Etiology

No one knows exactly what causes asthma. Much research has lead to....

### Theories:

- Hygiene theory (dirt is good)
- Allergens (cats, dust mites)
- Pollution (ozone)
- Infections (viral)
- Genetics
- Combinations of above

## History of Asthma



Asthma is a Greek word that is derived from the verb *aazein*, meaning to exhale with open mouth, to pant.

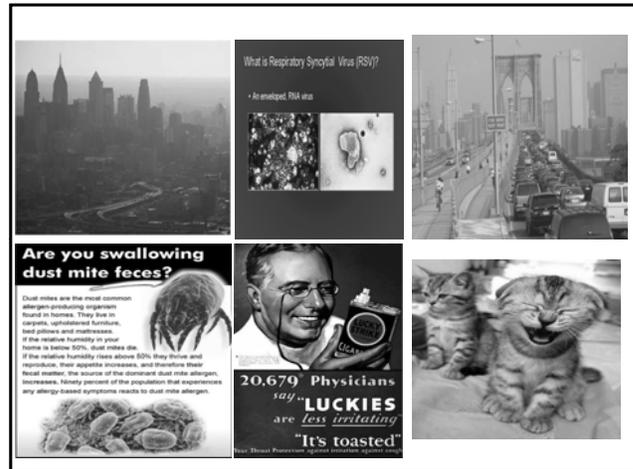
The *Corpus Hippocraticum*, by Hippocrates, is the earliest text where the word asthma is found as a medical term. It is uncertain whether Hippocrates (460-360 BC) meant asthma as a clinical entity or as merely a symptom. Hippocrates said spasm linked to asthma were more likely to occur among anglers, tailors and metalworkers.

## Asthma Pathogenesis

- **“Asthma” is actually a misnomer**
- **Inflammation in asthma is heterogeneous**
- **Multiple arms of the immune system are involved, Adaptive, Innate, and Humoral**
- **Several different phenotypes of asthma now defined by various inflammatory or clinical measures**

# Asthma Phenotypes

- **Sputum, Serum**
  - Allergic Th2, IgE, eosinophilic
  - Neutrophilic Th1+, neutrophils, also known as steroid resistant (refractory)
  - Mixed cellular
  - Paucigranular
- **Molecular**
  - Epithelial Gene Expression
  - “Levels” of pattern Th2 high v. Th2 low
- **Clinical**
  - Childhood onset, atopic
  - Adult onset, non atopic
  - Elderly
  - Exercise-induced
  - Female Asthma
- **Exhaled Nitric Oxide (eNO)**
- **Co Factors**
  - Smoking
  - Infection (viral)
  - Pollution



# Genetics

- Many candidates that appear in multiple studies
- Studies with larger numbers of people and long term longitudinal follow up will be needed to get some better insights on which genes are important
- Some of the current genes associated with asthma
  - Positionally cloned genes
    - DPP10, CYF1P2, HLAG, GPRA, SFRS8, PHF11, ADAM33
  - Genome-Wide Association Studies
    - CH13L1, ORMDL/GSDMB (childhood asthma), several common single nucleotide polymorphisms on chromosomes 2, 6, 9 and 22 among all asthmatics

(Postma, et al 2009, Moffat et al 2010)



**Sir John Floyer**, an English physician, credited with writing the first English language Treatise on asthma in 1698.

- Postulated that asthma was due to bronchoconstriction and not solely due to bodily humours
- Recognized the “several species of asthma” based solely on clinical history as the stethoscope was not yet invented.
- A good history goes a long way!

## Diagnosis of Asthma History is key



- Onset of asthma, history of exacerbations frequency and severity, hospitalizations, ICU, intubation
- Course of the symptoms (episodic)
- Key symptoms: wheeze, cough, dyspnea, chest tightness
- Typical episode – treatment and outcome
- Social/environmental setting
  - Where, when, precipitants (smoke, perfume, dust, mold, exercise, weather, pollution, menses)
  - Drugs (ASA, NSAID, Beer, Red Wine, Cocaine)
  - Allergy history
- Impact on patient/family (sex)
- Family history
- Review of systems (VCD, OSA, GERD, sinus, cardiac, edema, meds including herbals, alternative meds)

## EPR 3 Control v. Severity

The concepts of severity and control are used as follows for managing asthma:

- During a patient's **initial presentation**, if the patient is not currently taking long-term control medication, asthma **severity** is assessed to guide clinical decisions on the appropriate medication and other therapeutic interventions.
- Once therapy is initiated, the emphasis thereafter for clinical management is changed to the assessment of asthma **control**. The level of asthma control will guide decisions either to maintain or adjust therapy.

## NIH Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma (2007, 404 pages!)



<http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>

FIGURE 4-7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control	Classification of Asthma Control (≥12 years of age)		
	Well Controlled	Not Well Controlled	Very Poorly Controlled
Symptoms	≤2 days/week	>2 days/week	Throughout the day
Nighttime awakenings	≤2/month	3-30/month	>4/month
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EOs), S <sub>2</sub> , or peak flow	≤2 days/week	>2 days/week	Several times per day
Validated questionnaires			
ATAQ	8	5-7	3-4
AQOL	20-25*	11-13	5-9
ACT	20*	14-19	10
Exacerbations requiring oral systemic corticosteroids	0-1/year	≥2/year (see note)	
Risk	Evaluation requires long-term follow-up care		
Progressive loss of lung function	Evaluation requires long-term follow-up care		
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (see Figure 4-5 for treatment steps)	<ul style="list-style-type: none"> <li>• Maintain current step.</li> <li>• Regular follow-up every 3-6 months to maintain control.</li> <li>• Consider step down if well controlled for at least 3 months.</li> </ul>	<ul style="list-style-type: none"> <li>• Step up 1 step and reassess in 2-6 weeks.</li> <li>• For side effects, consider alternative treatment options.</li> </ul>	<ul style="list-style-type: none"> <li>• Consider short course of oral systemic corticosteroids.</li> <li>• Step up 1-2 steps and reassess in 2 weeks.</li> <li>• For side effects, consider alternative treatment options.</li> </ul>

## EPR 3 & Treatment

### 4 components of effective asthma management:

1. **Measures of assessment and monitoring**, obtained by objective tests, physical examination, patient history and patient report, to diagnose and assess the characteristics and *severity* of asthma and to monitor whether asthma *control* is achieved and maintained
2. **Education** for a partnership in asthma care
3. Control of *environmental* factors and *co morbid* conditions that affect asthma
4. **Pharmacologic** therapy

## Asthma Treatment Goals

- **Minimal use of short-acting inhaled beta agonist** (<1 x day, <1 canister per month)
- **Minimal or no adverse effects from medications** (lowest dose)
- **Meet patient and family expectations** regarding asthma care

## Asthma Treatment Goals

- **Minimal or no chronic symptoms** (cough, wheeze, p.m.)
- **Minimal or no exacerbations**
- **No limitations on activities:** no school/work missed
- **Maintain (near) normal pulmonary function**

## Asthma Pharmacotherapy

### 2 broad classes of asthma medications:

#### I. Quick relief medications

short acting beta-agonists  
anticholinergics

#### II. Long-term controller medications

corticosteroids  
leukotriene modifiers  
corticosteroids + long acting beta agonists  
anticholinergics  
methylxanthines  
cromolyn/nedocromil

## Corticosteroids

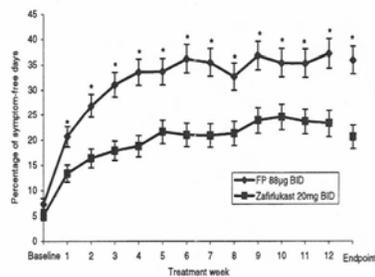
- Inhaled Corticosteroids (ICS) current mainstay of asthma therapy
- All the anti-inflammatory benefits of systemic agents with less side effects
- Recommended first-line therapy in all classes of asthma, mild to severe, except intermittent
- Asthma is NOT an “Advaair Deficiency”

## Long-acting $\beta$ -agonists (LABA)

- Salmeterol (Serevent) and Formoterol (Foradil)
- FDA issued a “black box” warning for long acting beta agonists, salmeterol (serevent) and formoterol (foradil)
- SMART study done by GSK demonstrated a trend toward increased deaths in African Americans with asthma treated ONLY with salmeterol

## Leukotriene Modifiers

- A Pill
- Works better than placebo
- DO NOT work as well as ICS
- DO NOT work as well as long acting beta agonists in combination with ICS



JACI (2000)105: 1123-1129

## LABA Story

- No data that in combination with an ICS there is an increase in deaths
- No one should be on a long acting beta agonist alone
- Close attention to AA patients treated with combination therapy, i.e. follow spirometry and symptoms closely.

## Omalizumab (Xolair)

- Monoclonal antibody v. IgE that prevents antigen-induced IgE from binding to mast cell
- Consider for severe asthma pts  $\geq 12$  yrs of age
- Evidence of perennial allergen sensitivity (dust mite, cat, etc)
- IgE level  $> 30$  IU/mL

## Bronchial Thermoplasty

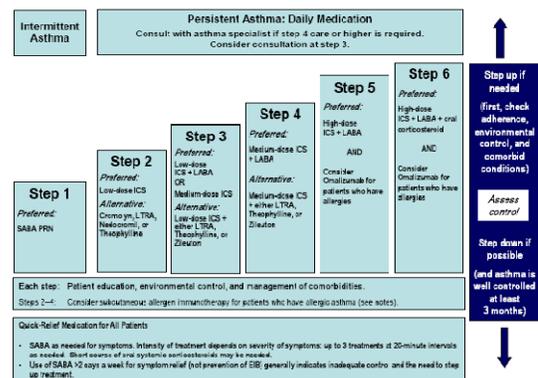
- FDA approved outpatient procedure that applies thermal energy directly to the airways via a bronchoscope to decrease airway smooth muscle
- Approved for severe asthmatics over age 18 who are currently stable
- Complete evaluation pre procedure is necessary
- Can improve asthma symptoms, ER visits and exacerbations in some severe asthmatics
- OSU Asthma Center has begun to do this procedure on select severe asthmatic patients



## Tiotropium Bromide (Spiriva)

- Peters, et al NEJM 2010
  - Tiotropium bromide (Spiriva) was superior to beclamethasone 160 mcg in terms of PEFR
  - Tiotropium bromide was non inferior to combination of beclamethasone and salmeterol
  - No safety concerns with tiotropium bromide
  - Larger trial with more clinical outcomes needed to determine where it may fit in treatment steps
- Anticholinergics may be of use in individual pts safe to give as a trial in non responsive patients

FIGURE 4-5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS  $\geq 12$  YEARS OF AGE AND ADULTS



## Summary

- Asthma is a major health problem worldwide
- We have come a long way in understanding the pathogenesis and developing effective treatments
- Much to learn with urgent research needs
- Next frontier focused on phenotyping patient's asthma with potential for more Personalized Treatments; ?  
Based on inflammatory profiles

## Other Information

- OSU Asthma Center:  
<http://www.asthma.osu.edu>
- ATS Virtual Asthma Center:  
<http://www.thoracic.org/clinical/asthma-center/index.php>
- CDC:  
<http://www.cdc.gov>

## Summary

- Currently focus on history, listen to how asthma is affecting your patient's life, seek co morbidities, adjust medications based on control
- Don't forget the basics: technique (HFA, spacer), compliance, cost, buy-in: if patient doesn't agree they won't do it
- Prepare (Action Plan) and educate patients on how to live a life without limits due to asthma

## The Ohio State University University Asthma Center

*"Where Research & Patient Care  
Come Together"*

The OSU Asthma Center

[www.asthma.osu.edu](http://www.asthma.osu.edu)



A Comprehensive Multi  
disciplinary Patient Care Clinic



A State of the Art Translational  
Research facility

**OSU Asthma Center  
Martha Morehouse Medical  
Plaza  
614-293-4925**

- *ICE Program: 3 Visit Individualized Asthma Treatment Program*
- *Refractory Asthma Program*
- *Asthma in Athletes Program*
- *Asthma in Women Program*
- *Asthma in Pregnancy Program*
- *Asthma Adolescent Transition Program*

**American Lung Association  
Asthma Clinical Research  
Network**

- **Multi Center Network**
- **Initiated in 1999 with 5 year grant from ALA**
- **19 original centers**
- **Renewed in 2004 and again in 2009**
- **20 current centers**



**The American Lung Association's Asthma Clinical  
Research Network**

***Mission: To improve asthma care through  
clinical research in diverse populations***



**ACRC Network  
Current Trials**

- **SOYA: Study of soy isoflavones for asthma**
  - ✓ **Randomized masked trial of soy tablet supplements v. placebo for asthma therapy in asthmatics age 12 years and older**
  - ✓ **Based on previous data from ACRC study suggesting soy intake is correlated with better lung function**
  - ✓ **Funding: ALA and NIH NHLBI**



## ACRC Network Current Trials

- **STAN: Study of asthma and nasal steroids**
  - ✓ Does treatment of rhinitis with nasal steroids improve asthma control in patients age 6 years and older
  - ✓ *Funding: ALA and NIH NHLBI*



## Asthma Care: Using What We Know

**Elizabeth D. Allen, M.D.**

Associate Professor, Clinical Pediatrics  
Nationwide Children's Hospital  
Ohio State University College of Medicine

## DO YOU HAVE ASTHMA?

The OSU Asthma Clinical Research Center is looking for volunteers to participate in Asthma Clinical Trials.

Participants may receive reimbursement to cover parking and for participation in a trial.

More information on our web page:  
[www.asthma.osu.edu](http://www.asthma.osu.edu)

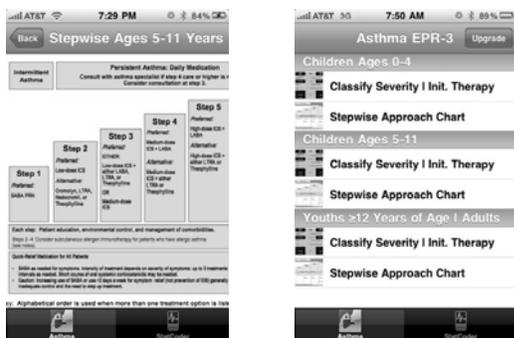
If interested, call David at (614)-293-4978 or  
1-800-678-6495  
or e-mail [Lung.Research@osumc.edu](mailto:Lung.Research@osumc.edu)

## What We Know

- **Initial NHLBI Guidelines Published in 1991**
- **Updated NHLBI Guidelines Published in 1997 and 2007**

## STAT Asthma NHLBI Guidelines

By Austin Physician Productivity, LLC



## Additional Steps of Recommended Care

- Educate patients
- Improve patient compliance
- Identify Triggers
- Environment modification
- Eliminate passive smoking



## Key Steps of Recommended Care

- Identify asthma severity (initially) and level of control (follow-up)
- Use Appropriate Controller Therapy
  - ✓ ICS therapy for all levels of persistent asthma
- Provide Asthma Action Plan (Written)

## Burden of Disease Remains High

- In 2007 in the United States
- 1.75 million asthma-related ED visits
  - 456,000 asthma hospitalizations
  - 3,447 deaths from asthma (>9/day)

## Contributors to Poor Outcomes

- Compliance Issues
- Environment Issues
- Under-diagnosis
- Under-treatment
- Under-education of Patients

## What We Do: WAP

- Utilization rates <50%
- Evidence of efficacy?

**Asthma Action Plan**

Name: \_\_\_\_\_ Date: \_\_\_\_\_

Sex: \_\_\_\_\_ Medication: \_\_\_\_\_

Primary Care Provider: \_\_\_\_\_

Triggers/Control: \_\_\_\_\_

Other: \_\_\_\_\_

**SILENCE** Use these daily preventive and reliever medications:

Medication	How Often	How Often

**CAUTION** Continue with your usual medicine and add:

Medication	How Often	How Often

**DANGER** Call your primary care provider:

Medication	How Often	How Often

## What We Do: ICS Use

- ICS usage rates – Median (range)
  - ✓ Moderate–severe persistent asthma: 32% (15 – 94%)
  - ✓ Severe persistent asthma: 69% (39-80%)
- Less ICS use seen in:
  - ✓ Minorities
  - ✓ Children

Pediatrics 2009; 123; S199-S204

## Ways to Improve

- Physician Education
- System Based Interventions

## Physician Education

- Important first step in improving outcomes
- Does not necessarily change practice



## A Pediatric Asthma Management Program

- 51 practices in towns & cities in Connecticut enrolled
- Program included core physicians champions and program coordinators
- Each office had lunch-time training, then follow-up visits
- Quarterly practice feedback

Cloutier MM, Wakefield DB, PEDIATRICS  
[www.pediatrics.org/cgi/doi/10.1542/peds.2010-1943](http://www.pediatrics.org/cgi/doi/10.1542/peds.2010-1943)

## System Interventions

- It's not just the Doc
- Establishment of a *routine*



## Easy Breathing Program: Screening

- Symptom Screening Questions
  - ✓ Wheezing
  - ✓ Nocturnal coughing
  - ✓ Exercise-induced respiratory symptoms
  - ✓ Persistent cough with colds
- Final diagnosis requires further history/clinical evaluation

## Easy Breathing Program: Severity

- Frequency of daytime and nighttime symptoms
- Exercise impairment
- Frequency of rescue medication use
- Effect on lifestyle/school attendance

## Asthma Video



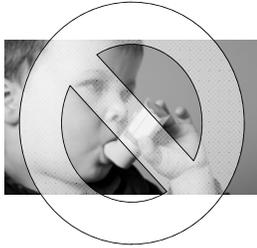
## Response to Findings

- Treatment regimen based on severity
  - ✓ Daily \*
  - ✓ Sick
  - ✓ Emergency
- Simple written action plan

## Correct Patient Instruction



## Correct Patient Instruction



## Outcomes

- Outcome analysis focused on the 77% of enrollees who received Medicaid
- These patients were more likely to:
  - ✓ Be younger
  - ✓ Have persistent asthma
  - ✓ Have greater exposure to smoke
  - ✓ Have greater exposure to roaches & rodents (less to dogs and cats)

## Correct Patient Instruction



## Outcomes: Guidelines

- Prescribed ICS use by children with persistent disease doubled (although fill rate did not change)
- Proportion of filled bronchodilator:ICS inhalers improved from 2.34 to 1.62

## Outcomes: Guidelines

- Prescriptions for leukotriene inhibitors and oral steroids increased
- WAP rates rose from <5% to >90%

## Incentives for Change



- The Right Thing to Do
- MOC Requirements
- Capitated Care Plans
- Pay for Performance

## Outcomes: Morbidity

	ED Visits	Hospitalization
Intermittent	No Change	↓ 40%
Persistent	↓ 23%	↓ 49%

Multi-variant analysis controlled for age, ethnicity, gender, season, year, asthma severity before and after enrollment