Asthma Diagnosis and Treatment in 2016
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Conflicts

• None
Outline/Objectives

- Case
- Prevalence
- Etiology
- Pathogenesis
- Phenotypes
- Therapy
B.B. is a 42 yr old AA Female Referred for Poorly Controlled Asthma

- Asthma onset at age 8
- 0 hosp stays since age 20, never intubated for asthma
- 4 ED visits past 6 months
- SOB with exertion, fumes, pollen, smoke, stress
- SOB, cough daily with occasional audible wheeze
- SABA not always effective for acute symptoms
- Montelukast (Singulair) “unsure if helped”
- Hx of GERD, Seasonal Rhinitis, Anxiety
- Exam normal
- CXR normal
- Spirometry with moderate obstruction, reversible with albuterol
- Exhaled Nitric Oxide 60 ppb (<25 ppb normal)
- Baseline labs unremarkable except for an IgE of 45 IU/mL (WNL) and blood eosinophils of 300/uL

Asthma is Common

- 2014 CDC data:
  - 18 million adults (7%)
  - 6 million children (9%)
- Sex, Race, SES are all significant variables

Summary National Health Survey 2014 (www.cdc.gov)
Asthma Can Kill

3,600 deaths in U.S.A in 2014

Summary National Health Survey 2014 (www.cdc.gov)

Etiology

• No one knows what causes asthma
• No one knows why the prevalence increased
• Theories:
  – Hygiene theory (dirt is good)
  – Allergens (cats, dust mites)
  – Pollution (ozone)
  – Infections (RSV)
  – Genetics
  – Combinations of above
Etiology

Asthma is not a single disease

Outline

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Asthma is an Inflammatory Lung Disease

Inflammation in asthma is heterogeneous


NIH Severe Asthma Research Program (SARP) Phenotypes

• Moore, et al used cluster analysis of over 700 participants in SARP trials and identified 5 clusters of asthmatics based on clinical and physiologic data
• Severe asthmatics existed in all clusters highlighting limitations of current classification
• Clusters differed in terms of over 34 factors including atopy, sex, eosinophils, etc but 80% of population could be accurately assigned to a cluster based on just 3 factors

Am J Respir Crit Care Med 2010;181:315–323
SARP Clusters

Cluster 1
Mild Allergic Asthma
Early onset; atopic; normal lung function ≤ 2 controller medications; minimal health care utilization minimal sputum eosinophilia

Cluster 2
Mild-Moderate Allergic Asthma
Most common cluster; early onset; atopic; borderline FEV1 but reverse to normal; ≤ 2 controller medications; low health care utilization, infrequent need for oral corticosteroids minimal sputum eosinophilia

Cluster 3
More Severe Older Onset Asthma
Older; very late onset; higher BMI (obese); less atopic; slightly decreased FEV1 with some reversibility; frequent need for oral corticosteroids despite ≤ 3 controller medications including high doses of inhaled corticosteroids; sputum eosinophilia

Cluster 4
Severe Variable Allergic Asthma
Early onset; atopic; severely decreased FEV1, but very reversible to near normal; high frequency of symptoms and albuterol use; "variable" with need for frequent oral corticosteroids; high health care utilization sputum eosinophilia

Cluster 5
Severe Fixed Airflow Asthma
Older; longest duration; less atopic; severely decreased FEV1 with less reversibility; COPD similarities; high frequency of symptoms and albuterol use despite oral corticosteroids; high health care utilization; co-morbidities Both sputum eosinophilia and neutrophilia

Molecular Phenotyping

- Woodruff, et al microarray and PCR analysis of bronchial brushings and biopsies from mild-moderate asthmatics and healthy controls and divided them by expression of IL-13 induced genes (TH2)
- Found 2 separate clusters: “TH2 high and TH2 low” asthma
- Correlations found with BHR, eosinophils, IgE
- Demonstrates molecular phenotype correlating with clinical and laboratory phenotypes

Am J Respir Crit Care Med 2009 Oct 15;180(8):796
Molecular Phenotype and Response to ICS

- Molecular phenotype correlating with clinical and laboratory phenotypes with demonstrable differences in response to therapy

WOW!
Asthma Phenotypes
Need lots more data

Clinical
• Age of onset
• Atopic (extrinsic)
• Non Atopic
• Obesity
• Exacerbations
• Severe (steroid dependent/resistance)
• Fungal Sensitivity
• Exercise-induced
• Aspirin Sensitive
• Menses Related
• Fatal/Near Fatal
• Tobacco Abuse
• Asthma COPD Overlap Syndrome (ACOS)

Sputum & Serum
• (Th2) eosinophils, IgE
• (Th1) neutrophils
• Mixed cellular
• Paucigranular

Molecular
• Epithelial Cell/Bronchial Wall Gene Expression
  – Th2 high v. Th2 low

Exhaled Nitric Oxide (eNO)
– <25 ppb
– >50 ppb

Severe Asthma Definition

Approach to Uncontrolled Asthma
Confirm Asthma Is The Culprit

• Adherence
  – Motivation/knowledge “Tell me when you take your inhalers”
  – Cost “Can you afford your medicines?”
• Inhaler technique
• Environmental issues in home/work
• Other medications (beta blocker, ACEi, et.)

It Really Is Asthma, BUT Is It Asthma Alone?
Co Morbidities as a Phenotype

• Vocal Cord Dysfunction
• GERD
• OSA
• Rhino sinusitis
• Depression/Anxiety
If you seek it, you will find it...........


Photo courtesy of Eric Forrest, MD

EPR3: GERD in Asthma

“Even in the absence of suggestive GERD symptoms, consider evaluation for GERD in patients who have poorly controlled asthma, especially with nighttime symptoms.... Treatment includes: ... using proton pump inhibitor medication.”

Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007. NIH, NHLBI. August 2007. NIH publication no. 08-4051.
GERD and Asthma

• **SARA – Study of Acid Reflux and Asthma**
  – RPCT of 412 participants funded by ALA/NHLBI
  – Treatment of asymptomatic GERD with PPI does not improve asthma control even if ph probe is positive

• **SARCA- Study of Acid Reflux in Children with Asthma**
  – RPCT of 306 participants funded by ALA/NHLBI
  – Treatment of asymptomatic GERD with PPI does not improve asthma control in children even if ph probe is positive
  – *JAMA* 2012 307(4): 373-381

Outline

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Phenotypes, blah blah blah

*What does this mean for the patient in my office today?*

- Initial evaluation should include a “phenotypic history”
- Low dose ICS remains best initial choice
- F/up in 6-12 weeks, if not controlled, increase to medium dose ICS or add LABA to the low dose ICS (patient preference, co pay, race)
- F/up in 6-12 weeks, if not controlled, increase to medium dose ICS/LABA
  - No data supports one v. another (Symbicort, Advair, Dulera, etc)
  - Fluticasone furoate/vilanterol (Breo) newest on block/TV, hyped on once a day dosing for compliance
- If all of these fail and **adherence, technique, environment, co morbidities** are all optimized then diagnosis of severe asthma is appropriate and additional clinical and laboratory phenotyping can assist with the next steps for therapy

### Phenotype Specific Therapy

- **Is it an allergic phenotype (Th 2)?**
  - Detailed allergy history, CBC for eosinophils, IgE, allergen testing including fungal sensitivity
  - Fractional exhaled nitric oxide (FeNO) >50ppb (ATS guideline 2011)
- **What was the response to steroids?**
  - Improvement but need oral or high dose ICS (severe/refractory)
  - No improvement (severe/refractory)
- **Fixed or reversible obstruction?**
  - Potential for thermoplasty or not
- **Do they have frequent exacerbations?**
  - Defined as >2/yr (ED/USHC/oral steroids) OR 1 hospitalization for asthma
- **Really, really certain it is asthma alone?**
  - Consider co morbidities 2-3 times
- **Do they smoke?**
  - Can impact therapy (ICS) and raises risk of COPD Overlap Syndrome
Allergic Phenotype
Non Responsive to ICS/LABA (severe)

FDA Approved Biologics:
• Omalizumab, anti IgE (Xolair)
  — SQ q 2-4 weeks based on IgE level, weight
• Mepolizumab, anti IL-5 (Nucala)
  — 100 mg SQ q 4 weeks
• Resilzumab, anti IL-5 (Cinqair)
  — 3 mg/kg IV infusion q 4 weeks
• More to come
• ? DOT for asthma

Omalizumab (Xolair)
FDA Approved 2003

• Monoclonal antibody v. IgE that prevents
  antigen-induced IgE from binding to mast cell
• Patients with moderate, severe asthma, 12 yrs or older
  who are inadequately controlled despite ICS
• Evidence of perennial allergic sensitivity (dust mite, cat,
  cockroach, mold)
• IgE level > 30 IU/mL but <700ish IU/mL (<330 lbs)
• Dose based on weight and IgE level, given SQ q 2-4
  weeks
Omalizumab (Xolair)

• Decreases exacerbations, improves asthma symptoms, allows for decrease in ICS use, allows for withdrawal of OS, improves QOL, limited effect on lung function, cost effective for high HCU-ing patients
• Risk of anaphylaxis, need an Epi Pen
• Cost: $10,000-$15,000/year

Mepolizumab (Nucala)
FDA approval November, 2015

• Monoclonal antibody v. IL 5
• Patients with severe asthma, 6 yrs or older
• Add on therapy for patients with frequent exacerbations and per FDA: “despite receiving their regular medications”
• Blood eosinophils of ≥ 150 cells/µL at initiation or history of ≥ 300 cells/µL in past 12 months
• 100 mg SQ q 4 weeks
Mepolizumab Asthma Exacerbations

Pavord, Lancet 2012
N = 621
40%-50% reduction

Ortega, NEJM 2014
N = 576
61% reduction

Mepolizumab (Nucala)

- Main impact on exacerbations, not consistently on symptoms, FEV1, AHR or QOL
- Cost: $32,500/year!
- Insurance coverage and requirements
Non Allergic Phenotype
Non Responsive to ICS/LABA (data limited)

- **Poor control Phenotype**
  - Leukotriene modifying agents
    - Montelukast (Singulair)
    - Zifirkulast (Accolate)
    - Zileuton (Zyflo CR)
    - Combinations
  - Tiotropium (Spiriva)
  - Theophylline (low dose)

- **Frequent exacerbations**
  - Macrolides
  - Bronchial Thermoplasty

- **ASA sensitive with polyps**
  - Desensitization

- **Smokers**
  - Leukotriene modifying agents
  - Tiotropium (Spiriva)
  - Theophylline (low dose)

Tiotropium Bromide (Spiriva)

- Peters, et al NEJM 2010
  - Tiotropium bromide was non inferior to beclamethasone/salmeterol for symptoms & lung function

- Wechsler, et al JAMA 2015
  - Open label, obese, 75% women, poor adherence
  - Tiotropium + ICS was equivalent to LABA + ICS in African American patients with asthma; no difference in AE

- September 2015, FDA approved Spiriva Respimat at 2.5 mcg/day for asthma (COPD 5 mcg/day)

- What phenotype might be benefit most?
  - Unclear
  - Add on to combination therapy
  - Smokers, Neutrophilic Phenotype?
  - COPD Overlap Syndrome?
**Macrolides**

- Several smaller trials suggest some asthmatics are chronically infected with mycoplasma or chlamydia (PCR) and benefit from clarithromycin (Biaxin) 500 mg bid for 8-16 weeks.
- However data is not definitive and not reproduced consistently.
- Have anti inflammatory properties as well.
- Large trial by Sutherland, et al NIH Asthma Clinical Network 2010 found no benefit in mild moderate uncontrolled asthmatics without PCR evidence of mycoplasma or chlamydia infection.
  - Very few (+) PCR, also few severe asthmatics in group.

**Macrolides**

- In pts with refractory non eosinophilic asthma phenotype azithromycin (250 mg/d) reduced exacerbations (Bruselle, et al Thorax 2013).
- May be of value in non allergic, frequent exacerbation phenotype or for shorter course in non allergic poor control phenotype.
- Need to monitor QTc, reversible hearing loss noted, and concerns for promoting resistance.
Bronchial Thermoplasty

- Deliver thermal energy to airway wall to decrease smooth muscle
- All visible and accessible airways (3-10mm) distal to main stem bronchi are treated except RML
- Series of contiguous activations
- 3 treatment sessions 3 weeks apart


Bronchial Thermoplasty

- Initial randomized study revealed some improvement in QOL but subsequent larger sham controlled trial was negative for the primary outcome of QOL but found a significant reduction in ER visits as a secondary analysis (Castro, et al 2010)
- Controversy ensued and continues about effectiveness (64% of sham had improved QOL)
- My opinion is the data is not clear and far from definitive. However, for phenotype of severe non allergic asthma with AHR and frequent exacerbations who fail other therapies or those severe allergic asthmatics with frequent exacerbations who fail biologics, it may be an option (their only option)
Alternative Agents

- **Vitamin D supplementation for asthma?**

- **Soy supplementation for asthma?**
  - No. (Smith, et al 2015 JAMA)

- **Exercise/Pulmonary Rehab: Limited data for asthma, limited insurance coverage, exercise is a good thing**

- **Acupuncture, herbal medicine, meditation, yoga...**
  - No consensus data to prove or disprove effectiveness
  - Placebo effect? Vocal Cord Dysfunction?

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Asthma Therapy Costs

“Can you afford your medicines?”

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Cost per month in Portland (retail)</th>
<th>Cost per Year in Portland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flovent 110</td>
<td>$200</td>
<td>$2400</td>
</tr>
<tr>
<td>Serevent</td>
<td>$300</td>
<td>$3600</td>
</tr>
<tr>
<td>Advair 110/21</td>
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<td>$3600</td>
</tr>
<tr>
<td>Symbicort 160/21</td>
<td>$300</td>
<td>$3600</td>
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<tr>
<td>Breo</td>
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<tr>
<td>Spiriva</td>
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<td>Montelukast</td>
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<td>Zafirlukast</td>
<td>$60</td>
<td>$720</td>
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<tr>
<td>Zylo CR</td>
<td>$1,500</td>
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</tr>
<tr>
<td>Theophylline</td>
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<td>$240</td>
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<tr>
<td>Relar</td>
<td>$1,000</td>
<td>$12,000</td>
</tr>
<tr>
<td>Nasale, et al</td>
<td>$2,700</td>
<td>$32,100</td>
</tr>
<tr>
<td>Bronchial Thermoplasty</td>
<td>$30,000</td>
<td>$360,000</td>
</tr>
</tbody>
</table>

www.goodRX.com
Conclusions

- Asthma is not a single disease
- Multiple phenotypes identified
- Clinical, laboratory phenotyping can assist with guiding therapy for patients who fail to respond to standard ICS/LABA therapy
- Additional studies are needed to improve phenotyping and evaluate specific therapies
- Drug costs may be a significant limitation to improving asthma outcomes especially for those individuals who appear to be suffering the most, i.e. the poor

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Case Follow-Up

- Poorly controlled severe persistent asthma with allergic phenotype, frequent exacerbations and clinical history concerning for VCD
  - low dose ICS, asthma education session with inhaler technique, spacer, written action plan, allergy testing
- After 6 weeks: still symptomatic, spirometry w mild obstruction eNO ↓35 ppb, (+) skin test to dust mite, cat, grass, trees
  - environmental control, antihistamine, stepped up to low dose ICS/LABA and referred for provocation VLS
- VLS: (+) VCD; speech therapy begun
- Returned in 6 weeks: Pt reports ability to differentiate VCD from asthma, symptoms <2 times/week, no nocturnal symptoms, exercising 3 times a week, no ED or missed work
- After 3 months able to step down from ICS/LABA to ICS alone
- If had failed would have been Xolair, Nucala candidate; possible BT if failed those

You Can Have Asthma And Be An Elite Athlete!
You Can Have Asthma And Sing!

You Can Have Asthma And Still Be Sexy!
Lets go Bucks!