Disclosures/Conflict of Interest

Grant support: NIH, NIAID, Centocor, Texas Ignition Fund Award

Speakers Bureau: Merck (resigned 2011)
### Trends of Asthma Morbidity/ Mortality

**ASTHMA**
- 20 million asthma sufferers in US  
  ~14 million are adult
- Lack of control is an enormous problem: healthcare costs = $14 billion/yr
- 10.4 million unscheduled physician office visits
- 1.8 million ER visits
- 0.5 million hospitalizations
- Asthma-related deaths > 10/day

**Emphysema**
- Prevalence > 2 million patients in the US  
  Annual estimated health care costs $1-5 billion
- Fourth leading cause of death  
  (120,000 deaths in year 2000); expected to be third leading cause by year 2020.
- By 2020, number of women dying > men
- Only disease among top 5 in which mortality is increasing
Why Are We Here?

- JB 16 y.o. senior honors student
  - Captain high school soccer team
  - “Well controlled” asthma
  - 6 days with nocturnal cough/used MDI 3-4 times/night
- School bus traveling to regional playoffs
- Severe asthma attack while traveling on farm-market road
- Died prior to arrival at local hospital
Why did this 16 year old girl die?

- She was on the “wrong side of the information gap”: just like 7/10 asthmatics

*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.

She was probably an "underperciever"

Poor Perception of Dyspnea (POD)

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

Multiple studies now that show underpercievers with life-threatening asthma may have a 20% mortality from asthma

ASTHMA 2012

• What have we learned?
• What are the controversies?
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 exacerbation
**ENO Measurement: ATS Guidelines**

- **< 25 ppb (20 ppb in children)** - eosinophilic inflammation and responsiveness to corticosteroids are less likely
- **> 50 ppb (> 35 ppb in children)** - eosinophilic inflammation and responsiveness to corticosteroids is more likely
- **25-50 ppb (20–35 ppb in children)** - gray zone and must use clinical judgment

Q: Does it help us clinically?
ASTHMA 2012

• Who needs daily therapy?
• How do we maximize therapy in severe asthma?
Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma: The BASALT Randomized Controlled Trial

End point – time to asthma worsening
- Continuous steroids vs. intermittent ICS/SABA: no difference
- Physician based adjustment vs. exhaled nitric oxide: no difference

Failure rate: 15% symptom based adjustment (patient decision)
22% physician based; 20% biomarker based

Mild to moderate asthma:
Duration – 36 weeks
N = 115/group
All on low dose ICS

JAMA. 2012;308(10):987-997
Critique of BASALT Study

• Study design
  – To determine superiority; not equivalence
  – Primary endpoint: AM peak expiratory flow rate
  – Not powered to assess differences in exacerbations
  – Drop out rate 21% (patients failing to comply with q6 wk. evaluation)

• Conclusions:
  – ICS/SABA may be effective in subgroups of asthmatics
  – Frequent assessment of biomarkers (FeNO) not supported
  – Ethnic differences noted (Hispanics – better with MD adjustments)
  – Strategy not appropriate for underpercievevers

JAMA. 2012;308(10):987-997
A Treatment Option for Severe Asthmatics

1. Short-acting Beta₂-agonists

2. Low-dose Inhaled Corticosteroids (ICS)

3. Low-dose ICS + Long-acting Beta₂-agonists (LABA) or Medium-dose ICS

4. Medium-dose ICS + LABA

5. High-dose ICS + LABA and Consider Omalizumab

6. High-dose ICS + LABA + Oral Corticosteroids and Consider Omalizumab

Alternatives Needed

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

• 2 RCTs with 912 subjects
  – All on ICS/LABA combination
  – FEV$_1$ < 80%
  – At least 1 "severe exacerbation" in prior year

• Clinical question: Would they benefit from LAMA?

• Study design:
  – Randomized to Tiotropium 5 µg "soft-mist inhaler"
  – Endpoints:
    • Time to first exacerbation
    • Peak/trough FEV$_1$
Results: ICS/LABA +/- Tiotropium

- Increased time to "severe" exacerbation from 226 to 282 days
- Overall 21% reduction in risk of "severe" exacerbation
- Mean change in FEV$_1$ = 86 ml in trial 1; 154 ml in trial 2

Seems like a very positive study!
Critique of Study

• Generalizability: subjects moderately severe (FEV₁ 55-61% at baseline) but very responsive to SABA (over 200 ml)

• Definition of "severe exacerbation" = need to double ICS for at least 3 days

• Secondary endpoints
  – No difference in symptom free days
  – No difference in Asthma QoL score
  – NNT to prevent one episode = 34

• Conclusion: may be of benefit to some asthmatics with frequent exacerbations if cost not an issue
Bronchial Thermoplasty: Treatment Method

- Shown to be "effective" in mild-moderate asthma
- All visible and accessible airways (3-10mm) distal to mainstem bronchi are treated
- Series of contiguous activations
- 3 treatment sessions
- AIR 2: RCT/sham controlled study in subjects with severe asthma (n= 288)

Treatment = radiofrequency ablation of smooth muscle in the airway

Bronchial Thermoplasty: AIR 2 study
Clinical Outcomes Summary at 1-Year*

- Improved asthma-related quality of life compared to control (AQLQ score)
- Improved clinical outcomes compared to control:
  - 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 due to asthma
- No unanticipated device-related adverse events

AIR 2: Data at 12 months

**Difference in AQLQ: Rx vs. Sham = 0.19 (N.S.)**

**No difference in:**
- FEV1 or PEFR
- Rescue medication; symptom free days
Conclusions: AIR 2 study

• Compared to sham control, thermoplasty reduced:
  – "Severe" exacerbations & E.D. visits
  – Missed days of school/work

• Bronchial thermoplasty is costly and resulted in hospitalization rate of 8.4% during protocol

• Hospitalizations were usually 1-2 days

• Bronchial thermoplasty
  – Approved by the FDA for severe asthma (age ≥ 18 yrs old)
  – May improve outcomes in subject failing optimal Rx
  – Unclear which asthma phenotype will benefit
Update in Asthma 2012

- **What reduces exacerbations of asthma**
  - Environmental tobacco smoke (ETS) = strongest predictor of respiratory illness in children
    - Ban on ETS in Scotland decreased asthma hospitalization by 18.2%
  - Exercise can reduce bronchospasm
    - 3 months of *aerobic exercise training* significantly improved asthma QOL and asthma free days (p=0.001)

- **Medication compliance: Is QD really better that BID?**
  - Indacaterol – once a day LABA
  - Ciclosenide – once a day high potency ICS

- **MOST IMPORTANT: Allergan Avoidance**
  Most forgotten component in asthma education by MD
COPD 2012

• What have we learned about COPD?
Basics of Treating COPD: 2012

• Initiation of long-acting bronchodilator
  – Canadian guidelines suggest cost-effective to start with either LABA (salmeterol/formoterol) or LAMA (tiotropium/aclidinium)
    • Less exacerbations & better quality of life
    • Much better compliance

• Inhaled Corticosteroids: Risk vs. Benefit
  • Risk: Increase risk of pneumonia with RR= 1.6
  • Benefit: FEV$_1$ < 50 % or "asthma/atopic" features with eosinophils, frequent exacerbations, or positive BD test

• Home oxygen
  • Saturation $\leq 88\%$ (or $\leq 89\%$ with Cor Pulmonale)
  • **Must** wear oxygen 16 hours/day for survival benefit
GOLD Guidelines 2012: Assess Symptoms

MRC: easy; ≥ grade 2
- More aggressive Rx
- **Problem:** only assesses dyspnea

COPD Assessment Test (CAT): 8-item measure of health status impairment in COPD
- Assesses dyspnea, cough, sputum production
- Correlates well with SGRQ (St. George Respiratory Questionnaire)

http://catestonline.org
Global Strategy for Diagnosis, Management and Prevention of COPD

**Combined Assessment of COPD**

Assess risk of exacerbations next

- **(A)**: mMRC 0-1 or CAT < 10 (30% risk)
- **(B)**: mMRC > 2 or CAT > 10 (20% risk)
- **(C)**: FEV\(_1\) ≥ 50% and only 0 or 1 exacerbations per year (10% risk)
- **(D)**: FEV\(_1\) < 50% or two or more exacerbations per year (40% risk)

**Risk (Exacerbation history)**

- 0: Low Risk (A or B)
- ≥ 2: High Risk (C or D)

**Symptoms (mMRC or CAT score)**

- mMRC 0-1 or CAT < 10
- mMRC > 2 or CAT > 10
**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Manage Stable COPD: Pharmacologic Therapy**

*(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)*

<table>
<thead>
<tr>
<th>Patient</th>
<th>First choice</th>
<th>Second choice</th>
<th>Alternative Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA</td>
<td>PDE4-inh. SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS and LAMA or ICS + LABA and LAMA or ICS + LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Controversy: Role of Azithromycin in COPD

- **Azithromycin for Prevention of Exacerbations of COPD**
  - RCT for 1 year (n = 1142)
  - Moderate-severe COPD
  - Azithro 250 mg QD

- **Results**
  - Time to exacerbation: 266 vs 174 days* 
  - SGRQ reduced 2.8 vs. 0.6
  - Exacerbations 1.48 vs 1.83/pt .yr.* (*p < 0.01)

- **Follow-up NEJM: Recommended all COPD patients with > 1 exacerbation be placed on Azithro**

- **Today: Azithro 250mg 3x/week very common “add-on” therapy**

---

**Critique of Article:**
- All patients – nl QT, nl hearing
- Greater hearing deficit
- Increase bacterial resistance noted
- Stage 4 COPD (LABA/ACS/LAMA) no benefit

---

*N Engl J Med 2011;365:689-98*
The Key to Treating COPD: Smoking Cessation

- Smoking cessation (Lung Health Study)
  - Reduced all cause mortality (MI/Cancer)
  - Only therapy proven to prevent ↓ FEV$_1$
  - Average smoker quits 5 times prior to success
GOLD Pharmacologic Treatment Options

**Bronchodilators**
- **Short-acting**
  - β-agonists
    - Albuterol
    - Levalbuterol
    - Pirbuterol
    - Anticholinergic
      - Ipratropium
    - Combination
      - Combivent
  - Theophylline
- **Long-acting**
  - β-agonists
    - Salmeterol
    - Formoterol
    - Arformoterol
    - Indacaterol
  - Anticholinergic
    - Tiotropium
    - Aclidinium
  - Phosphodiesterase inhibitor
    - PDE-4 Inhibitor
    - Roflumilast

**Anti-inflammatory**
- **Corticosteroids**
  - Combination
    - Salmeterol + Fluticasone
    - Formoterol + Budesonide
- **Phosphodiesterase inhibitor**
  - PDE-4 Inhibitor
  - Roflumilast
Roflumilast: PDE4- inhibitor

- Selection of patients who will benefit:
  - Severe COPD with chronic bronchitis
  - On LABA/ICS and LAMA
  - Exacerbation requiring steroids/hospitalization

- Mechanism of action: anti-inflammatory medication

- Benefits: reduced exacerbations

- Side effects:
  - Nausea/diarrhea (10 – 20%)
  - Weight loss (7.5%)
  - Anxiety/depression (6%)