Update on Asthma & COPD

Case #1 - Asthma

- MN is a 48 year-old female with lifelong asthma
- Triggers: cats, grasses, mold, URIs
- Occasionally wheezes
- FEV1 50-100% of predicted
- Albuterol, FP/SM 500/50, Montelukast
- Does Well x 2-3 months, then crashes (Sxs, ED, Hosp)
- Doesn't take FP/SM because she's terrified of steroids

Question #1 - Asthma

What can you tell her that may be helpful?

1. Modern ICS are safe
2. As long as you take a LABA as well, ICS are safe
3. ICS effects (good and bad) are dose-dependent
4. Nobody needs to take ICS forever

Disclosures

- No Pharma Consulting, Research, Lectures
- NHLBI - Asthma Clinical Research Network
- NHLBI AsthmaNet
- NHLBI - COPD Clinical Research Network
- NAEPP Coordinating Committee
- NHLBI SPIROMICS
What is the current role of Inhaled Corticosteroids in Asthma?

ICS Dose Response and Side Effects

- Most benefits occur at low-medium dose
- Minimal additional improvement with high dose
- Few adverse events seen at low-medium dose
- Risk increases with high-dose

Factors associated with diminished dose-response
- Genetic Polymorphisms
- Obesity
- Smoking
- Vitamin D Insufficiency
- Severe Asthma

ICS Dose Response and Side Effects

ICS Side Effects

Local Side Effects:
- Hoarseness
- Candidiasis
- Cough
- Dysphonia

Systemic Side Effects:
- HPA Suppression
- Cushing Syndrome
- Osteoporosis
- Cataracts
- Dermal Thinning
- Adrenal Insufficiency
- Growth Suppression

High-dose ICS is Associated with Hospitalization for Adrenal Insufficiency

N = 1,410,211 patients Quebec, Canada
Rx: Bronchodilator, Cromolyn, LTRA, or ICS 1990 – 2005
N = 368,238 "Prevalent Users" (>3x/year)
N = 392 Hospitalized for Adrenal Insufficiency
Nested case-control analysis

Lapi, Kezouh, Suissa, Ernst

<table>
<thead>
<tr>
<th>Cumulative Dose (tertiles)</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60,000 mcg</td>
<td>15.1</td>
<td>12.5</td>
<td>1.59</td>
<td>1.25</td>
<td>(0.83-1.87)</td>
</tr>
<tr>
<td>60-157,000 mcg</td>
<td>15.3</td>
<td>11.1</td>
<td>1.59</td>
<td>0.96</td>
<td>(0.60-1.52)</td>
</tr>
<tr>
<td>&gt;157,000 mcg</td>
<td>15.3</td>
<td>6.3</td>
<td>3.57</td>
<td>1.90</td>
<td>(1.07-3.37)</td>
</tr>
</tbody>
</table>

ICS in asthma or COPD is not associated with new onset diabetes mellitus or hyperglycaemia.

Budesonide: 26 trials Asthma; n=14,993
8 trials COPD; n = 8259

All ICS, Asthma: 60 trials; n = 36,269

Treatment with inhaled corticosteroids in patients with asthma or COPD was not associated with increased risk of new onset diabetes mellitus or hyperglycaemia.

O’Byrne et al. Respir Med 2012 Nov;106(11):1487-93

NAEPP GUIDELINES

“If there is a clear and positive response for at least 3 months, a careful step down in therapy should be attempted to identify the lowest dose required to maintain control. (Evidence D)”

Evidence D = Panel Consensus Judgment

GINA GUIDELINES

"Controller treatment may be stopped if the patient’s asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occurs for 1 year (Evidence D)"

Evidence D = Panel Consensus Judgment

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Minimize ICS Dose By:

- Start low, then Step Up
- Step down if well-controlled x 2-3 months
- Use Patient-Centric Measures to gauge Control (Symptoms, Rescue, ACT)
- Consider/Tolerate Intermittent ICS for mild-moderate asthma
- Consider alternatives to ICS

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Question #2 - Asthma

What keeps you from "stepping down"?

1. I don’t know how, or what to monitor
2. I see stable patients so infrequently it’s hard to assess or remember
3. Guilty feet have got no rhythm

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Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma

The BASALT Randomized Controlled Trial

Calhoun et al. JAMA. 2012;308(6):575-576
Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma: The BASALT Randomized Controlled Trial

No significant differences among the 3 treatment groups.

<table>
<thead>
<tr>
<th>Baseline to End Treatment</th>
<th>P=0.904</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bud</td>
<td>5.0 ± 0.5</td>
</tr>
<tr>
<td>Zaf</td>
<td>6.0 ± 0.5</td>
</tr>
<tr>
<td>PRN</td>
<td>6.0 ± 0.5</td>
</tr>
</tbody>
</table>

**Should all patients with asthma be treated regularly with an inhaled corticosteroid?**

The IMPACT Study

**Change in AM Peak Flow**


Asthma Exacerbation Rates  
(symptoms warranting course of oral CS)

![Graph showing asthma exacerbation rates](image)


### Intermittent vs Daily ICS for Persistent Asthma in Children and Adults

- **4 Pediatric Trials**
- **2 Adult Trials**
- **N = 1211 patients**

**No Difference**
- Daily ICS
- Oral Corticosteroids
- Severe Adverse Health Events

**Daily ICS**
- Better Lung Function
- Less Airway Inflammation
- Better Asthma Control
- Less Reliever Use
- Modest Growth Suppression

_Chauhan et al. Cochrane Database of Systematic Reviews 2012 Issue 12, Art. No.: CD009611_

### Risk of Asthma Exacerbation after Stopping Low-Dose ICS

Systematic Review & MetaAnalysis
- **N = 7 studies**

**For Subjects who Stopped ICS (stable x 4 weeks):**
- **Asthma Exacerbation**  
  - **RR = 2.35 (CI, 1.88-2.92)**
- **Decreased FEV1**
- **Decreased AM PEF**
- **Increased Asthma Symptom Scores**
- **No difference in Asthma Specific Q of L**

**No difference in ED or Hospitalizations**

_Rank MA et al. J Allergy Clin Immunol 2013 [Epub ahead of print]_

### Case #2 - Asthma

- **MN** is a 48 year-old female with lifelong asthma
- **Triggers:** cats, grasses, mold, URIs
- **Occasionally wheezes**
- **FEV1 70% of predicted**
- **Albuterol, FP/SM 500/50, Montelukast**
- **Frequent Sxs, ED, Hospitalization, Prednisone**
- **Skin Bruises, Low Bone Density, Cushingoid**
Not all asthma is the same!!

(Heterogeneity)

(Phenotypes)

A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic

- Asthma is a heterogeneous disease
- ~50% of asthmatics – poor response to steroids
- Eosinophilic airway inflammation not ubiquitous
- Prior ACRN data (n=995; 2.7 SI; ≥2% eos):

Sputum Eosinophil Percentage (No ICS)


TH2 Genes Overexpressed in Asthma

Woodruff et al Am J Respir CCM 180:388, 2009
**Increase in FEV₁ after Fluticasone is seen only in TH₂-high group**

![Graph showing increase in FEV₁ after Fluticasone]

Woodruff et al. Am J Respir CCM 180:388, 2009

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**Summary - ICS in Asthma**

- ICS are 1st line treatment
- Most benefits at low-moderate dose
  - Few AEs at low-moderate dose
- Significant/Serious side effects do occur
- "Step Treatment" is still the Standard
- Increase ICS dose, but be prepared to decrease if there's no obvious benefit
- Stopping ICS may be associated with worsening control, including exacerbations, but does not appear to increase ED or hospitalizations

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**Guidelines for Management of COPD**

- Consider "Symptom-Based Treatment" (Intermittent)
- Eosinophilia is not ubiquitous
- Non-eosinophilic asthma is not steroid responsive
- Consider non-ICS alternatives
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>
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<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 or LABA and PDE4-inh. or SABA and SAMA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS + LABA and LAMA or ICS + LABA and PDE4-inh. or LABA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>

Question #3 - COPD
Which of the following is true?

1. Every patient with cough and sputum should have spirometry
2. Spirometry can help guide treatment
3. Spirometry may have prognostic value
4. All of the above

COPD Dx & Management Guidelines
American College of Physicians
American College of Chest Physicians
American Thoracic Society
European Respiratory Society

<table>
<thead>
<tr>
<th>Sxs</th>
<th>FEV1</th>
<th>Intervention</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td>Spirometry</td>
<td>Should Not</td>
<td>Strong, Mod Qual</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>Spirometry</td>
<td>Should</td>
<td>Strong, Mod Qual</td>
</tr>
<tr>
<td>Yes</td>
<td>60-80%</td>
<td>Bronchodilator</td>
<td>May</td>
<td>Weak, Low Qual</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt;60%</td>
<td>Bronchodilator</td>
<td>Should</td>
<td>Strong, Mod Qual</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt;60%</td>
<td>LABA or LAMA</td>
<td>Should</td>
<td>Strong, Mod Qual</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt;60%</td>
<td>Combination Rx</td>
<td>May</td>
<td>Weak, Mod Qual</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt;50%</td>
<td>Pulmonary Rehab</td>
<td>Should</td>
<td>Strong, Mod Qual</td>
</tr>
<tr>
<td>?</td>
<td>PO2&lt;55; SpO2&lt;88</td>
<td>Long-term O2</td>
<td>Should</td>
<td>Strong, Mod Qual</td>
</tr>
</tbody>
</table>

Diagnosis of COPD
- Definition: FEV1/FVC < 0.70
- Physical Exam:
  >90% Specificity
  Poor Sensitivity
- Best Predictor:
  >40 Pack Year Smoking History
  Positive Likelihood Ratio (LR) 12 [95% CI, 2.7-50]
- > 55 Pack Years
- Wheezing on Auscultation
- Self-reported wheezing (LR) 156

Qaseem et al

Simel and Rennie
Evidence-based Clinical Diagnosis
Screening for Airflow Obstruction

- No benefit of screening adults with no symptoms
- No evidence that treating asymptomatic individuals prevents future symptoms, or reduces the subsequent decline in lung function.
- Spirometry is useful to identify symptomatic patients with airflow obstruction who may benefit from pharmacotherapy.


Screening for Airflow Obstruction

- Regardless of COPD Risk Factors: NO DATA to support benefit of screening patients with NO RESPIRATORY SYMPTOMS
- Mixed (unconvincing) data on smoking cessation
- Low FEV1/FVC at screening is associated with high rate of decline in FEV1 (Burrows et al, Am Rev Respir Dis 135:1987)
- Smoking cessation slows progressive loss of lung function (Anthonisen et al, 1994).

Therapy Reduces the Rate of Decline In Postbronchodilator FEV1


LABA vs ICS + LABA? Exacerbations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log(RR) ratio</th>
<th>SL Weight</th>
<th>N, Randomized</th>
<th>95% CI</th>
<th>Year</th>
<th>Rate ratio</th>
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</thead>
<tbody>
<tr>
<td>LABA vs ICS</td>
<td>-0.67</td>
<td>0.0734</td>
<td>13.4%</td>
<td>0.92 [0.61, 1.08]</td>
<td>2009</td>
<td></td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.4309</td>
<td>0.073</td>
<td>13.5%</td>
<td>0.65 [0.66, 0.75]</td>
<td>2009</td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.61</td>
<td>0.044</td>
<td>16.8%</td>
<td>0.88 [0.84, 0.93]</td>
<td>2009</td>
<td></td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.3038</td>
<td>0.038</td>
<td>11.8%</td>
<td>0.70 [0.69, 0.83]</td>
<td>2009</td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.3624</td>
<td>0.091</td>
<td>11.8%</td>
<td>0.70 [0.59, 0.83]</td>
<td>2009</td>
<td></td>
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<tr>
<td>LABA vs ICS</td>
<td>0.77 [0.66, 0.89]</td>
<td>66.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02, Chi² = 21.64, df = 4 (p = 0.0002), I² = 82%
Test for overall effect: Z = 3.56 (p = 0.0004)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log(RR) ratio</th>
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<th>N, Randomized</th>
<th>95% CI</th>
<th>Year</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA vs ICS</td>
<td>-0.26</td>
<td>0.135</td>
<td>0.1%</td>
<td>0.77 [0.60, 0.99]</td>
<td>2003</td>
<td></td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.254</td>
<td>0.12</td>
<td>0.4%</td>
<td>0.75 [0.69, 0.84]</td>
<td>2003</td>
<td></td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.257</td>
<td>0.15</td>
<td>7.5%</td>
<td>0.79 [0.69, 0.92]</td>
<td>2008</td>
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<tr>
<td>LABA vs ICS</td>
<td>-0.4942</td>
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<td>7.5%</td>
<td>0.61 [0.40, 0.92]</td>
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<tr>
<td>LABA vs ICS</td>
<td>0.73 [0.64, 0.83]</td>
<td>66.6%</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02, Chi² = 19.02, df = 3 (p = 0.039), I² = 93%
Test for overall effect: Z = 3.56 (p = 0.0004)

Total (95% CI) | 100.0% | 0.76 [0.66, 0.84] |
Figure 4. Forest plot of comparison: Combined inhalers versus long-acting beta-agonists (primary outcome), outcome: 1.1 Exacerbation rate (combined treatment versus beta-agonists).
### Screening for Airflow Obstruction

**Do medications slow progression of asymptomatic airflow obstruction?**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>[No Data]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Risks of Screening

- **Cost**
- **Follow-up of False Positives**
- **Anxiety**
- **Reassurance of Smokers with Normal Results**

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### LABA vs ICS + LABA? Mortality

<table>
<thead>
<tr>
<th>Combination</th>
<th>Odds Ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image]</td>
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<td></td>
</tr>
</tbody>
</table>

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### LABA vs ICS + LABA? Pneumonia

<table>
<thead>
<tr>
<th>Combination</th>
<th>Odds Ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Question #4 – COPD**

Which are important for Prognosis?

1. FEV1
2. History of Exacerbations
3. Symptoms
4. Current smoking status
5. All of the above

**Natural History of COPD**

- Patients with COPD lose lung function faster than normals
- Smoking cessation decreases rate of loss
- Patients with reversibility lose lung function faster than those without reversibility
- Patients with emphysema lose lung function faster than those with chronic bronchitis

**Changes in FEV1 over time in COPD**


- N = 2163 with COPD
- 40-75 years old
- >10 Pack Years
- FEV1/FVC < 0.7
- FEV1 <0.8
- Followed x 3 years

- 38% >40 ml/yr
- 31% 21-40 ml/yr
- 23% -20 to +20 ml/yr
- 8% > 20 ml/yr

Mean rate of change: -33 ± 2 ml/yr

**GOLD (2007) Classification of COPD Severity**

- FEV1/FVC < 0.70
- GOLD 1: (Mild COPD) FEV1 > 80% predicted
- GOLD 2: (Moderate COPD) FEV1 50-80% predicted
- GOLD 3: (Severe COPD) FEV1 30-50% predicted
- GOLD 4: (Very Severe COPD) FEV1 <30% predicted

GOLD Guidelines 2007
COPD Assessment: A New Model

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.

GOLD Guidelines 2013

Exacerbations:
1 → A and A → D

Mortality:
A ≻ C ≻ B ≻ D
(more sx/s = greater mortality)

Mortality from CVD and Cancer:
B ≻ A
D ≻ C

Patient Category | Characteristics | Spirometric Classification | Exacerbations per year | mMRC | CAT
--- | --- | --- | --- | --- | ---
A | Low Risk, Less Symptoms | GOLD 1-2 | ≤1 | 0-1 | <10
B | Low Risk, More Symptoms | GOLD 1-2 | ≤1 | ≥2 | ≥10
C | High Risk, Less Symptoms | GOLD 3-4 | ≥2 | 0-1 | <10
D | High Risk, More Symptoms | GOLD 3-4 | ≥2 | ≥2 | ≥10

GOLD 2011 - Prognosis

Copenhagen City Studies
- 5,919 Heart Study
- 55,731 Population Study
- 6,628 Individuals with COPD
- Follow up (to 8.9 years, mean 4.3)

Lange et al
Am J Respir Crit Care Med 186:976, 2012
### Manage Stable COPD: Pharmacologic Therapy

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

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- Routine follow-up is essential
- Lung function can be expected to worsen over time, even with the best available care
- Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify complications
- Decline in lung function is best tracked by **spirometry** performed at least once a year to identify patients whose lung function is declining quickly.

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Global Strategy for Diagnosis, Management & Prevention of COPD, Updated, 2013