Asthma/COPD Update with Inhaler Workshop

October 8, 2017

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Disclosures

- None
Agenda

- Asthma Updates
- COPD Updates
- Inhaler Workshop
Asthma Updates
Asthma Updates

- SMART Trial aftermath
- Guidelines (GINA, ERS/ATS)
- FeNO testing
- Biologics
SMART

• 2006: The Salmeterol Multicenter Asthma Research Trial

• Compared salmeterol vs. placebo added to usual care

• Subjects:
  • 26,355 patients
  • >12 years of age

SMART Findings

• No significant difference between the two for:
  • Overall safety
  • Respiratory-related deaths (50 vs 36)
  • Life-threatening experiences

• HOWEVER..................

Salmeterol Is Evil

- Small increase in respiratory-related deaths (24 vs 11)
- Small increase in asthma-related deaths (13 vs 3)
- Majority were in African-Americans (20 vs 5)/(19 vs 4)
- All were statistically significant
- So based on 15 more patients deaths with salmeterol from this subset population...

Innocent Bystanders

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta₂-adrenergic agonists (LABA),** such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. A U.S. trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. (5.1)

- **Prescribe SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.** Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. **Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.** (1.1, 5.1)

- **Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.** (5.1)
• Evaluated tiotropium vs. LABA in addition to inhaled corticosteroids (ICS) in black population over 18 months
  • Tiotropium + ICS \((n = 532)\)
  • LABA + ICS \((n = 538)\)

BELT Findings

• No difference in clinical outcomes, including \( \text{FEV}_1 \)

• No significant difference with non-asthma and asthma-related adverse effects \( (P = 0.16) \)
  
  • 3 deaths occurred, all in tiotropium group

AUSTRI

- Evaluated safety of adding salmeterol to fluticasone in adults and adolescents (ages ≥12)
  - Fluticasone only ($n = 5834$)
    - Black ($n = 856; 15\%$)
  - Fluticasone + salmeterol ($n = 5845$)
    - Black ($n = 870; 15\%$)

AUSTRI Findings

- Asthma exacerbations
  - Fluticasone only \((n = 597)\)
  - Fluticasone + salmeterol \((n = 480)\)
    - Adding salmeterol reduced exacerbations 16-32%
- Asthma exacerbations in black patients
  - Fluticasone only \((n = 79)\)
  - Fluticasone + salmeterol \((n = 79)\)

VESTRI

• Evaluated safety of adding salmeterol to fluticasone in children (ages 4-11)
  • Fluticasone only \( (n = 3101) \)
    • Black \( (n = 511; 16.5\%) \)
  • Fluticasone + salmeterol \( (n = 3107) \)
    • Black \( (n = 539; 17.3\%) \)

VESTRI Findings

- Asthma exacerbations
  - Fluticasone only ($n = 309$)
  - Fluticasone + salmeterol ($n = 265$)
- Asthma exacerbations in black patients
  - Fluticasone only ($n = 21$)
  - Fluticasone + salmeterol ($n = 27$)

VESTRI Findings

- Serious asthma-related events
  - Fluticasone only ($n = 21$)
  - Fluticasone + salmeterol ($n = 27$)
- No deaths!
- Salmeterol + fluticasone is non-inferior to fluticasone alone
- Correlates to AUSTRI findings in children

Is There A Class Effect?

- Salmeterol vindicated? What about formoterol?
- NEJM 9/1/2016: Evaluated safety of adding formoterol to budesonide (ages ≥12)
  - Fluticasone only \( n = 5766 \)
    - Black \( n = 407; 6.9\% \)
  - Fluticasone + salmeterol \( n = 5785 \)
    - Black \( n = 396; 6.8\% \)

Study Findings

- Risk of asthma exacerbation
  - Budesonide only ($n = 633, 10.8\%$)
  - Budesonide + formoterol ($n = 539, 9.2\%$)

- Asthma-related deaths
  - Budesonide only ($n = 0$)
  - Budesonide + formoterol ($n = 2, <0.1\%$)

Overall Findings

- No evidence that LABA on top of inhaled corticosteroid increases risk of asthma-related death
- No data on lone LABA compared to ICA or ICA + LABA
GINA Stepwise Approach
### Box 8. Low, medium and high daily doses of inhaled corticosteroids (mcg)

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Adults and adolescents</th>
<th>Children 6–11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Beclometasone dipropionate (CFC)*</td>
<td>200–500</td>
<td>&gt;500–1000</td>
</tr>
<tr>
<td>Beclometasone dipropionate (HFA)</td>
<td>100–200</td>
<td>&gt;200–400</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>200–400</td>
<td>&gt;400–800</td>
</tr>
<tr>
<td>Budesonide (nebules)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclesonide (HFA)</td>
<td>80–160</td>
<td>&gt;160–320</td>
</tr>
<tr>
<td>Fluticasone furoate (DPI)</td>
<td>100</td>
<td>n.a.</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
<td>100–250</td>
<td>&gt;250–500</td>
</tr>
<tr>
<td>Fluticasone propionate (HFA)</td>
<td>100–250</td>
<td>&gt;250–500</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>110–220</td>
<td>&gt;220–440</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400–1000</td>
<td>&gt;1000–2000</td>
</tr>
</tbody>
</table>

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant. *Included for comparison with older literature.
FeNO

- Fractional concentration of exhaled nitric oxide
  - Modestly associated with eosinophilic airway inflammation
  - Can be seen in other eosinophilic states w/o asthma
  - Not elevated in neutrophilic asthma phenotype
  - Decreased in smokers
  - Does not help rule in or out asthma
FeNO cont.

- Recommended neither by GINA nor ERS/ATS
  - ERS/ATS 2014: “We suggest that clinicians do not use FeNO in addition to clinical criteria to guide therapy in adults or children with severe asthma (conditional recommendation, very low quality evidence).”¹
  - GINA 2017: “At present, neither sputum- nor FENO-guided treatment is recommended for the general asthma population.” (Evidence A)²

# FeNO Interpretation: ICS Naïve

## Clinical Guide to Interpretation of FeNO Values

<table>
<thead>
<tr>
<th>FeNO Value (ppb), Patients ≥12 years of age</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>25-50</td>
<td>&gt;50</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FeNO Value (ppb), Patients &lt;12 years of age</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>20-35</td>
<td>&gt;35</td>
<td></td>
</tr>
</tbody>
</table>

In the case of a >40% increase from previously stable levels, interpret as high FeNO.

**Consider as significant increase in FeNO**
- Increase >10 ppb from last measurement
- Increase >20% from last measurement

**Interpretation with respect to steroid response**

- **Unlikely to respond to corticosteroids**
  - Anxiety/Hyperventilation
  - Cardiac disease
  - COPD
  - GERD
  - Nonasthmatic asthma
  - Rhinosinusitis
  - Vocal cord dysfunction
  - Cystic fibrosis
  - Primary ciliary dyskinesia (FeNO <5 ppb)

- **May respond to corticosteroids** (interpret cautiously in clinical context)
  - High levels of allergen exposure
  - Infection as a reason for worsening symptoms

- **Highly likely to respond to corticosteroids**
  - Atopic asthma
  - High-levels of allergen exposure
  - Infection as a reason for worsening symptoms
  - COPD with mixed inflammatory phenotype
  - Eosinophilic bronchitis

**Possible Alternate Diagnoses**

- Smoking has been shown to reduce FeNO levels.

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*COPD = chronic obstructive pulmonary disease; FeNO = fractional exhaled nitric oxide; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid.

*Interpretations of levels based on patient having symptoms (cough and/or wheeze and/or shortness of breath) present during the past 6+ weeks.*
FeNO Interpretation: On ICS

**CLINICAL GUIDE TO INTERPRETATION OF FeNO VALUES**

| MANAGEMENT OF PATIENTS DIAGNOSED WITH ASTHMA, TREATED WITH ICS OR COMBINATION THERAPY |
| :--: | :--: | :--: |
| **FeNO value (ppb), patients ≥12 years of age** | **LOW** | **INTERMEDIATE** | **HIGH** |
| <25 | 25-50 | >50 |
| <20 | 20-35 | >35 |

In the case of a >40% increase from previously stable levels, interpret as high FeNO.

| Consider as significant increase in FeNO | Increase >10 ppb from last measurement | Increase >10% from last measurement |
| Consider as response to ICS | Decrease >10 ppb from last measurement | Decrease ≥20% from last measurement |

**SYMPTOMATIC**
- Review symptoms and consider alternate diagnoses
- Possible inadequate ICS treatment
  1. Check adherence
  2. Check for poor inhaler technique
  3. Consider adding other therapy apart from ICS (e.g., LABA)
  4. Consider ICS dose increase

**ASYMPTOMATIC**
- Implies patient is adherent to treatment
- Consider dose reduction, or in case of current low ICS dose, consider ICS withdrawal all together (repeat FeNO 4 weeks later to confirm this judgement; if it remains low, relapse is unlikely)
- No change in ICS dose if FeNO trend is stable over time
- Check for poor inhaler technique
- Check for poor inhaler technique
- No change in ICS dose if FeNO trend is stable over time
- Check adherence
- Check for poor inhaler technique
- Check for poor inhaler technique

**ADDITIONAL CONSIDERATIONS**
- Aspirin/IBP responsiveness
- Cardiac disease
- COPD
- GERD
- Neuroendocrine asthma
- Rhinosinusitis
- Vocal cord dysfunction
- Cystic fibrosis
- Primary ciliary dyskinesia (FeNO <5 ppb)

Also consider:
- High levels of allergen exposure
- Infection as a reason for worsening symptoms
- High levels of allergen exposure
- Infection as a reason for worsening symptoms

FeNO tests using NIOX MINO* are reimbursable, CPT 95612

*NIOX MINO is a registered trademark.
Biologics In Asthma

- Omalizumab (Xolair®)
- Mepolizumab (Nucala®)
- Reslizumab (Cinqair®)
Omalizumab

- Anti-IgE antibody
  - For patients who failed ICS
  - Baseline IgE 30-700 IU/mL
    - Limited information in treatment >700 IU/mL
    - Note: 1 IU/mL = 2.5ng/mL
Omalizumab cont.

- Goal is to reduce IgE <10 IU/mL
- Cannot use IgE levels to monitor; levels increase due to IgE-anti-IgE complexes
- May take up to 1 year for IgE levels to decrease
- Issues:
  - Anaphylaxis
  - Questionable increased cancer risk
    - Developed soon after starting therapy – pre-existing?
Mepolizumab, Reslizumab

• Interleukin-5 (IL-5) antibody
  • IL-5 responsible for differentiation and growth of eosinophils

• Mepolizumab
  • Eosinophil count ≥150 cells/μL within 6 weeks of therapy
  • Eosinophil count ≥300 cells/μL within past 12 months

• Reslizumab
  • Eosinophil count ≥400 cells/μL
COPD Updates
COPD Updates

- GOLD 2017
- Azithromycin in COPD
- Asthma-COPD overlap syndrome
GOLD 2017

Global Initiative for Chronic Obstructive Lung Disease

POCKET GUIDE TO COPD DIAGNOSIS, MANAGEMENT, AND PREVENTION
A Guide for Health Care Professionals
2017 REPORT
# GOLD Scales

### Table 2.4. Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV₁)

<table>
<thead>
<tr>
<th>GOLD 1:</th>
<th>Mild</th>
<th>FEV₁ ≥ 80% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2:</td>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>GOLD 3:</td>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>GOLD 4:</td>
<td>Very Severe</td>
<td>FEV₁ &lt; 30% predicted</td>
</tr>
</tbody>
</table>

### Table 2.5. Modified MRC dyspnea scale

**Please tick in the box that applies to you (one box only) (Grades 0–4)**

- **mMRC Grade 0.** I only get breathless with strenuous exercise.
- **mMRC Grade 1.** I get short of breath when hurrying on the level or walking up a slight hill.
- **mMRC Grade 2.** I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
- **mMRC Grade 3.** I stop for breath after walking about 100 meters or after a few minutes on the level.
- **mMRC Grade 4.** I am too breathless to leave the house or I am breathless when dressing or undressing.
GOLD ABCD

Figure 2.4. The refined ABCD assessment tool

Spirometrically confirmed diagnosis

Assessment of airflow limitation

Exacerbation history

Assessment of symptoms/risk of exacerbations

- FEV₁ (% predicted)
  - GOLD 1: ≥ 80
  - GOLD 2: 50-79
  - GOLD 3: 30-49
  - GOLD 4: < 30

- mMRC 0-1
  - CAT < 10
- mMRC ≥ 2
  - CAT ≥ 10

Post-bronchodilator FEV₁/FVC < 0.7

A
B
C
D
GOLD Treatment Algorithm

Group C
- LAMA + LABA
- LABA + ICS
- Further exacerbation(s)
- LAMA

Group D
- Consider roflumilast if FEV₁ < 50% pred. and patient has chronic bronchitis
- Consider macrolide (in former smokers)
- Further exacerbation(s)
- LAMA + LABA + ICS
- Persistent symptoms/further exacerbation(s)
- LAMA
- LABA + ICS

Group A
- Continue, stop or try alternative class of bronchodilator
- Evaluate effect
- A bronchodilator

Group B
- LAMA + LABA
- Persistent symptoms
- A long-acting bronchodilator (LABA or LAMA)
Azithromycin in COPD

- Macrolides have anti-inflammatory properties
- Evaluated number of exacerbations of azithromycin 250mg daily vs placebo (n = 1577)
  - Placebo: 1.83 exacerbations/year
  - Azithromycin: 1.48 exacerbations/year
  - \( P = 0.01 \)
- Concern about QTc prolongation/cardiac issues

Azithromycin & Cardiac Risk

- Cohort evaluated 3,546,239 patients between those who took:
  - No antibiotics \((n = 1,391,180)\)
  - Amoxicillin \((n = 1,348,672)\)
  - Azithromycin \((n = 347,795);\) over 5 days
  - Ciprofloxacin \((n = 246,626)\)
  - Levofloxacin \((n = 193,906)\)

Small increased risk of cardiovascular death with azithromycin (not significantly different from levofloxacin, but significantly greater than ciprofloxacin)

Most pronounced in patients with underlying cardiovascular disease

Does Azithromycin Increase Risk?

- Different cohort from Denmark evaluated 2,204,469 azithromycin prescriptions compared to no antibiotic use and penicillin V
- No increased risk of cardiovascular death with azithromycin compared to penicillin
  - In fact, penicillin had more cardiac deaths (146 vs. 17) and azithromycin had a -1 adjusted absolute risk of cardiac death
Asthma-COPD Overlap

- Continuum of obstructive diseases, not just separate entities
- Features of both COPD and asthma
  - Asthma can have negative bronchodilator response
  - COPD can have positive bronchodilator response
- Not defined by GINA or GOLD
- Multiple definitions by other organizations

One Attempt At Diagnosis

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Persistent airflow limitation (post-bronchodilator FEV1/FVC &lt;0.70 or LLN) in individuals 40 years of age or older; LLN is preferred</td>
<td>1. Documented history of atopy or allergic rhinitis</td>
</tr>
<tr>
<td>2. At least 10 pack-years of tobacco smoking</td>
<td>2. BDR of FEV1 ≥200 mL and 12% from baseline values on 2 or more visits</td>
</tr>
<tr>
<td>OR equivalent indoor or outdoor air pollution exposure (e.g. biomass)</td>
<td></td>
</tr>
<tr>
<td>3. Documented history of asthma before 40 years of age</td>
<td>3. Peripheral blood eosinophil count of ≥300 cells·μL⁻¹</td>
</tr>
<tr>
<td>OR BDR of &gt;400 mL in FEV1</td>
<td></td>
</tr>
</tbody>
</table>

The committee recommends presence of all three major criteria and at least one minor criterion for asthma-chronic obstructive pulmonary disease overlap syndrome. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; BDR: bronchodilator response using 400 ug of albuterol/salbutamol (or equivalent); LLN: lower limit of normal.

“The Five Commandments”

- 1) “A patient with asthma may develop non-fully reversible airflow obstruction but this is not COPD, not even ACO; it is obstructive asthma.”
- 2) “A patient with asthma who smokes may also develop non-fully reversible airflow obstruction, which differs from obstructive asthma and from ‘pure’ COPD. This is the most frequent type of patient with ACO.”

3) “Some patients who smoke and develop COPD may have a genetic Th2 background (even in the absence of a previous history of asthma) and can be identified by high eosinophil counts in peripheral blood. These individuals could be included under the umbrella term of ACO.”

“The Five Commandments”

4) “A patient with COPD and a positive bronchodilator test (>200 mL and >12% FEV$_1$ change) has reversible COPD but is not an asthmatic, or even ACO.”

5) “A patient with COPD and a very positive bronchodilator test (>400 mL FEV$_1$ change) is more likely to have some features of asthma and could also be classified as ACO.”

Inhaler Workshop
Inhaler Workshop

• Discuss factors when selecting inhaled medication
• Review currently available delivery devices
• Hands-on session
Goals for Inhalation

- Deliver drug to respiratory mucosa
- Minimize systemic absorption
Factors Affecting Delivery

- Drug/formulation-related
- Device-related
- Patient/disease-related

Drug/Formulation Issues

- Drug potency
- Pharmacokinetics
- Particle size
- Propellant
- Additives
- Viscosity

Device Issues

- Deposition properties
- Particle size
- Ease of use
- Accuracy of dosage
- Administration apparatus

Patient/Disease Issues

- Inspiratory flow rate
- Upper airway anatomy
- Lower airway obstruction
- Patient preference & adherence
- Ability to use device
- Competency

Remember This?
Chlorofluorocarbons (CFCs)

- Used as propellants in aerosols
  - Also refrigerants and solvents
- Destroyed ozone layer
- Montreal Protocol on Substances that Deplete the Ozone Layer
  - September 16, 1987
  - Phase out CFCs
Inhalers: Ozone Killers!

- FDA phased out generic albuterol as of 12/31/2008
- Newer albuterol products use hydrofluoroalkane (HFA)
- Available then as now:
  - ProAir HFA
  - Proventil HFA
  - Ventolin HFA
- $$$ and still no generics...

The Only Good Casualty
Delivery Systems

- Diskus®
- Ellipta®
- Flexhaler®
- HandiHaler®
- NeoHaler®
- Pressair®
- RespiClick®
- Respimat®
- HFA
- Nebulizer
Diskus®

- Flovent®
  - Fluticasone propionate
- Serevent®
  - Salmeterol
- Advair®
  - Fluticasone propionate + Salmeterol
Ellipta®

- Arnuity®
  - Fluticasone furoate
- Incruse®
  - Umeclidinium
- Anoro®
  - Umeclidinium + Vilanterol
- Breo®
  - Fluticasone furoate + Vilanterol
Flexhaler®

- Pulmicort®
  - Budesonide
HandiHaler®

- Spiriva®
  - Tiotropium
NeoHaler®

- Arcapta®
  - Indacaterol
- Seebri®
  - Glycopyrrolate
- Utibron®
  - Indacaterol + Glycopyrrolate
Pressair®

- Tudorza®
  - Aclidinium
RespiClick®

- ProAir®
  - Albuterol
Respimat®

- Spiriva®
  - Tiotropium
- Striverdi®
  - Olodaterol
- Stiolto®
  - Tiotropium + Olodaterol
- Combivent®
  - Albuterol + Ipratropium
HFA

- ProAir®
  - Albuterol
- Proventil®
  - Albuterol
- Ventolin®
  - Albuterol
- Xopenex®
  - Levalbuterol
Nebulizer

- Albuterol
- Ipratropium
- DuoNeb®
  - Albuterol + Ipratropium
- Brovana®
  - Arformoterol
- Perforomist®
  - Formoterol
- Pulmicort Respules®
  - Budesonide
Device Selection Summary

- Chose drug(s)
  - Based on GINA/GOLD guidelines
  - Clinical history
  - Dosing regimen

- Chose delivery system
  - Is patient able to use it physically?
  - Mental competence?

- Is it covered by insurance?
Why Care About Teaching?

- You can get paid for it!
- CPT: 94664
- Document!
- My example: “I personally instructed the patient on the use of [Inhaler Name]. Appropriate technique was demonstrated. Questions answered. Sample provided to patient.”
Inhaler Workshop

Hands-On Session