Asthma Management Updates:
A Focus on Long-acting Muscarinic Antagonists and Intermittent Inhaled Corticosteroid Dosing

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Disclosures
- I have been contracted with AHRQ through the EPC program, including sponsorship through the NHLBI
- I have a current contract with AHRQ through the EPC program
- I have been funded through grants from Merck, Pfizer, The Intersocietal Accreditation Commission and The American Pharmacists Association
- I will be speaking of off label indications today

Learning Objectives
- Explain the efficacy of long-acting intermittent muscarinic antagonists (LAMA) and intermittent inhaled corticosteroids (ICS) on health outcomes associated with asthma
- Recognize the asthma “step” in which LAMA or intermittent ICS therapy may be appropriate
- Describe key counseling points for the Respimat delivery device

Question 1
The concept of SMART therapy in asthma is described as
a. Providing adherence monitoring for inhalers to assure optimal compliance
b. Delivery of ICS and LABA simultaneously as rescue and controller medication
c. Self-adjusted dosing of maintenance asthma medications at home
d. Immunotherapy for concurrent asthma and allergic rhinitis

Question 2
LAMA are currently recommended by guidelines for which patients:
- Persistent asthmatics 12y and older as add-on to standard of care
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Question 3
All of the following are true regarding Respimat except
a. The device self-locks after designated doses are actuated
b. There is no need for hand eye coordination
c. Tiotropium is available through this delivery device
d. Preparing the inhaler requires some level of strength to insert the canister
Guidelines for Asthma Management

  - Expect an update within the next year regarding four core topics: LAMA, intermittent ICS, FeNO and immunotherapy
- Global Initiative for Asthma (2017)

Pathophysiology

- Asthma is a **chronic inflammatory** disorder of the airway in which many cells and cellular elements play a role
- Variable and recurring symptoms of wheezing, cough, breathlessness, and chest tightness that are **reversible**
- Caused by airflow obstruction from
  - **Underlying inflammation**
  - Bronchial hyper-responsiveness
  - Bronchoconstriction
  - Airway edema and remodeling

Long-Term Goals of Care

- **Reduce impairment**
  - Prevent chronic and troublesome symptoms
  - Require SABA use ≤2d/wk for quick relief, excluding prevention of exercise-induced asthma
  - Maintain near normal pulmonary function and activities of daily living
  - Meet parent’s and families expectations
- **Reduce risk**
  - Prevent exacerbations and need for ER visits or hospitalizations
  - Prevent loss of lung function and in children, growth
  - Optimize pharmacotherapy while reducing adverse events

Pharmacologic Management Options

**Initial Controller**
- ICS
- LABA, LAMA
- Montelukast, theophylline

**Reliever/Rescue**
- SABA

**Severe Asthma**
- Biologics
- Oral steroids

Inhaled Corticosteroids (ICS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dosage forms</th>
</tr>
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<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>QVAR MDI</td>
<td>MDI</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort Flexhaler Generic</td>
<td>DPI, NEB</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Alvesco MDI</td>
<td>MDI</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Aerospan MDI</td>
<td>MDI</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flovent HFA, Flovent Diskus</td>
<td>DPI, MDI</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Auranex Tailshaler</td>
<td>DPI</td>
</tr>
</tbody>
</table>

ICS Indications in Asthma

- Reduce asthma symptoms, increase lung function, improve QOL, reduce risk of exacerbations, asthma related hospitalizations and death
- Traditionally dosed on a scheduled, daily basis in addition to a SABA pm as the rescue medication

GINA

- Persistent asthma defined as SABA use or daytime symptoms ≥2 days/wk or more nighttime awakenings per month, interference with ADLs, reduced FEV1 predicted ≤20%
- Symptoms or SABA ≥2 times/m
- Waking due to asthma ≥1 times/m

Symptoms plus risk factors for exacerbations including low lung function, exacerbation requiring steroids, ICS for asthma
EPR-3 Stepwise Approach for Managing Asthma ≥12y

1. **Assess control**
   - Step 1: PRN SABA
   - Step 2: Controller
   - Step 3: PRN SABA or low dose ICS/formoterol
   - Step 4: Med/high dose ICS; low dose ICS + LTRA or theophylline
   - Step 5: Add tiotropium
   - Step 6: High dose ICS + LTRA or theophylline

GINA Stepwise Approach for Managing Asthma ≥12y

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   - Step 3: PRN SABA or low dose ICS/formoterol
   - Step 4: Med/high dose ICS; low dose ICS + LTRA or theophylline
   - Step 5: Refer for add-on treatment (i.e. tiotropium, anti-IL5, anti-IgE)

Single Maintenance and Reliever Therapy (SMART) or Single Inhaler Therapy (SIT)

- Use of an inhaler containing both an ICS and the LABA formoterol to be used as the controller and reliever inhaler
  - Dulera (mometasone and formoterol) MDI
  - Symbicort (budesonide and formoterol) MDI
  - Neither are currently licensed in the US for this indication

- Formoterol has an onset similar to salbutamol and duration similar to salmeterol
- To provide quick symptom relief when needed, but also quickly increase maintenance medication doses upon symptom deterioration (when albuterol would otherwise be used by the patient)

Does Symbicort DPI vs. MDI matter?


Symbicort DPI vs. MDI

- Table 2: Therapeutic equivalence of budesonide/formoterol DPI and budesonide/formoterol pMDI

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Adjusted mean difference</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
<td>Budesonide/formoterol pMDI vs. budesonide/formoterol DPI</td>
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*Therapeutic equivalence not defined at a level of 95% CI for the difference in mean FEV1 between budesonide/formoterol DPI and budesonide/formoterol pMDI.*
A Summary of SMART Trial Characteristics

<table>
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<tr>
<th>Characteristics</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Population</td>
<td>Mostly 16 yr of age with mild (&lt;50% FEV₁) uncontrolled asthma taking daily ICS (prednisone equivalent dose) ± LABA (e.g., formoterol, salmeterol), or ≥1 exacerbation in the prior year for enrollment.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Exclusively budesonide/formoterol (200/6 mcg) DPI combination as controller and reliever. Generally use max of 12 puffs in 1 day.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Budesonide with SABA prn at an equivalent or higher ICS dose. Budesonide/formoterol with SABA prn at an equivalent or higher ICS dose. Little data reflecting other ICS or ICS/LABA combinations.</td>
</tr>
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<td>Outcomes</td>
<td>Mainly focused on composite exacerbation outcomes and death. Less evaluation of asthma symptom scores, symptoms, quality of life.</td>
</tr>
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Evidence for SMART Compared to ICS+LABA Maintenance

- Much less studied than in comparison to ICS+LABA
- Similar trends in data suggesting that SMART
  - Reduces the risk of exacerbations compared to ICS alone at the same or higher dose
  - Does not impact mortality rate differently than ICS

Evidence for SMART Compared to ICS Maintenance

- Overall ICS exposure in some studies is higher with SMART but with the trade off of lower systemic exposure for exacerbations
- Adverse events frequencies in individual trials is similar between SMART and control groups

Safety of SMART

- No significant differences in serious adverse events between SMART and control groups.
GINA Recommendations for SMART ≥12y

LAMA and Asthma

- LAMA provide bronchodilation through an alternative mechanism of action compared to standard of care treatments
- Tiotropium was FDA approved for asthma maintenance therapy in patients 12y and older in 2015, the indication was for the SMI expanded to 6y and older in 2017

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<tr>
<td>Tiotropium</td>
<td>Spiriva Respimat 1.25mcg</td>
<td>SMI DPI</td>
</tr>
<tr>
<td></td>
<td>Spiriva 18mcg</td>
<td></td>
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A Summary of LAMA Trial Characteristics

Add-on LAMA- Evidence in Adults

Add-on LAMA in Younger Patients

- Adolescents 12-17y
  - Moderate, uncontrolled asthma: Improved FEV1 and trends towards improved symptom control and QOL at 48w when tiotropium was added to ICS vs. placebo; no difference in exacerbations
  - Severe, uncontrolled asthma: Positive trends in improved lung function and asthma symptoms at 12w when tiotropium was added to ICS + another controller vs. placebo; no difference in exacerbations
- Children 6-11y
  - Moderate, uncontrolled asthma: Improved spirometry at 24w when tiotropium was added to ICS with or without another controller
  - Children 1-5y
    - Safety profile is consistent with all older patients
GINA Recommendations for LAMA ≥12y

Respirmat Delivery Device

Example of Respirmat Inhaler

Respirmat Counseling- Steps Prior to First Use

Respirmat Counseling- Daily Use – T.O.P

Summary

- Current GINA guidelines recommend SMART therapy as equally preferred option to ICS+LABA and SABA PRN in step 3 or 4 asthma in patients 12y and older
  - Will EPR-3 update adopt these similar recommendations?
- Current GINA guidelines recommend LAMA as add-on therapy to ICS and LABA in patients 12y and older
  - EPR-3 update may include suggestions as alternate to LABA?
  - Will the guidelines adopt use in younger patients?
- More drugs are becoming available with Respirmat technology
  - Offers advantages of soft mist and lock out mechanism
  - Still requires coordination of breathing
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Thank you for your attention!