Asthma Update 2018

Jennifer W. McCallister, MD, FACP, FCCP
Associate Professor
Division of Pulmonary, Critical Care, and Sleep Medicine
The Ohio State University Wexner Medical Center

Disclosures

I have no professional or personal financial conflicts of interest to disclose.
Objectives

- Discuss important safety considerations in asthma care
- Describe asthma-COPD overlap
- Understand role of phenotyping in the care of the patient with severe asthma

Case

- 28 year old male presents for asthma follow-up
- Denies nocturnal symptoms
- Uses albuterol 2-3 times/month prior to basketball
- No exacerbations in the past year
- Current medications
  - Beclomethasone 80 µg 2 puffs twice daily
  - Nasal fluticasone
  - As needed albuterol
Case cont.

- Spirometry
  - FEV1/FVC 0.82
  - FEV1 82% predicted
- Exam unremarkable
- What changes would you make in his asthma therapy?

Stepping down therapy

- Inhaled corticosteroids (ICS) in mild/moderate patients can usually be reduced by 50%
- Complete cessation of ICS not advised
- Strategies for Long-acting beta agonists (LABAs)/ICS less clear

Rank et al. JACI 2013; 131:724.
Safety considerations for long-acting beta-agonists

December 20, 2017

Food and Drug Administration (FDA) removed the *Boxed Warning* from the drug labels of products containing both ICS and LABAs

https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm; accessed 3/7/2018

Salmeterol Multi-center Asthma Research Trial (SMART)

- Large placebo-controlled US study of salmeterol vs. placebo added to usual asthma therapy
- Increase in asthma-related deaths
  - Salmeterol group: 13 deaths in 13,176
  - Placebo: 3 deaths in 13,179
  - RR 4.4 [CI 1.2-15.3]

Salmeterol Multi-center Asthma Research Trial (SMART)

- Increase in asthma related deaths in African Americans
- “Usual asthma care” often deviated from guideline
- 47% of participants prescribed ICS
  - 49% Caucasians
  - 39% African Americans


FDA meta-analysis 2008

110 studies with 60,954 subjects

43% of all subjects from SMART

LABAs associated with increased risk of composite endpoint

Levenson, M. United States Food & Drug Administration, November 12, 2008.
Deaths & intubations

<table>
<thead>
<tr>
<th>No ICS</th>
<th>ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>43/44 (0.19%)</td>
<td>1/44 (0.01%)</td>
</tr>
<tr>
<td>n=22,286</td>
<td>n= 7,862</td>
</tr>
</tbody>
</table>

Levenson, M. United States Food & Drug Administration, November 12, 2008.

FDA mandated safety studies

- 5 Randomized controlled trials
  - Four ages > 12 (n = 11,700 in each)
  - One ages 4-11 (n = 6,200)
- 2011-2017
- 26 weeks duration
- Outcomes
  - Hospitalizations, intubation, death
FDA mandated safety studies

- ICS + LABA vs. ICS—Adult
  - Fluticasone/salmeterol
  - Budesonide/formoterol
  - Mometasone/formoterol
  - Formoterol + fluticasone [individual devices]—not completed
- ICS + LABA vs ICS—Pediatric
  - Fluticasone/salmeterol

Meta-analysis of serious asthma-related events in patients ≥ 12 years

<table>
<thead>
<tr>
<th>Event</th>
<th>ICS/LABA (n=17,537)</th>
<th>ICS (n=17,552)</th>
<th>ICS/LABA vs ICS Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious asthma related events</td>
<td>116</td>
<td>105</td>
<td>1.10 (0.85, 1.44)</td>
</tr>
<tr>
<td>Asthma-related deaths</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asthma-related intubations</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Asthma-related hospitalizations</td>
<td>115</td>
<td>105</td>
<td></td>
</tr>
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</table>

https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm; accessed 3/7/2018
Where does this leave us?

- When used in combination with ICS, LABAs do not significantly increase the risk of serious asthma-related events
- *Boxed Warning* remains for single agent LABAs

How should this influence treatment decisions?

Asthma
Never use LABA without ICS

COPD
Start treatment with LAMA and/or LABA, without ICS

What if overlap exists?

Asthma-COPD overlap

Distinguishing asthma from COPD can be difficult

Not a single disease i.e. not a syndrome

Identified in clinical practice by features shared with both asthma and COPD

Clinical features assist with diagnosis

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Before 20 years</td>
<td>• After 40 years</td>
</tr>
<tr>
<td>• Variable symptoms</td>
<td>• Persistent symptoms</td>
</tr>
<tr>
<td>• Clear triggers</td>
<td>• Cough &amp; sputum unrelated to triggers</td>
</tr>
<tr>
<td>• Variable obstruction</td>
<td>• Persistent obstruction</td>
</tr>
<tr>
<td>• History of atopy</td>
<td>• Heavy tobacco exposure</td>
</tr>
<tr>
<td>• No progression; variation in symptoms</td>
<td>• Slowly progressive</td>
</tr>
</tbody>
</table>

Role of spirometry

Reversible airflow limitation
FEV1/FVC < 0.7 post-BD

Initiate therapy based on predominant symptoms

Asthma
- Start ICS
- Add LABA and/or LAMA
- Do not use LABA without ICS

COPD
- Start LAMA and/or LABA alone or in combination
- Do not use ICS without LABA and/or LAMA

Balanced
- Initiate therapy targeted at asthma
- Start ICS and add LABA and/or LAMA as needed

Cases

**Patient 1**
- 56 year old male
- Adult onset asthma
- No family history of allergies
- Nasal polyps, eosinophilic sinus disease s/p multiple surgeries
- FEV1/FVC 0.46, FEV1 51%
- Poorly controlled on LABA/ICS with multiple exacerbations

**Patient 2**
- 48 year old woman
- Adult onset asthma
- BMI 34 mg/kg²
- No family history of allergies
- GERD, OSA
- FEV1/FVC 0.73, FEV1 74%
- Poorly controlled on LABA/ICS with multiple exacerbations

The asthma umbrella

Real world phenotypes

- Atopic/early onset asthma
  - Allergic symptoms
  - Elevated IgE

- Late onset eosinophilic
  - Polyposis, sinusitis
  - Steroid refractory eosinophilia

- Obesity related
  - Lack of Th2 markers
  - Symptom burden, comorbidities

Role of tiotropium in asthma: a systematic review with meta-analysis

- Tiotropium as add-on to ICS
  - Improved PEF, FEV1
  - Reduced exacerbations, improved control
- Tiotropium + ICS vs LABA + ICS
  - Not inferior to salmeterol
- Tiotropium as add-on to LABA + ICS
  - Improved PEF, FEV1
  - Reduced exacerbations, improved control

Rodrigo et al. CHEST 2015; 147:388.
TH₂ mediated processes in airways


Biologics in the treatment of asthma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Anti-IgE</td>
<td>Prevents binding to receptor on mast cells and basophils</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Anti-IL-5</td>
<td>Prevents binding to eosinophils</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Anti-IL-5</td>
<td>Prevents binding to eosinophils</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>Anti-IL-5</td>
<td>Binds to IL-5 receptor to cause eosinophil apoptosis</td>
</tr>
</tbody>
</table>
### Real world phenotypes & treatment options

**Atopic/early onset asthma**
- Corticosteroid responsive
- Omalizumab

**Late onset eosinophillic**
- Corticosteroid refractory
- Anti-IL 5

**Obesity related**
- Manage comorbidities
- Target smooth muscle

### Cases

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Interim summary

- Consider risk/benefit ratio of discontinuing ICS in well controlled asthma
- Awareness of asthma-COPD overlap can facilitate treatment decisions
- Evolving asthma phenotyping will guide asthma care in more severe disease

What’s New in Pediatric Asthma

Elizabeth D. Allen, MD
Pediatric Pulmonary Medicine
Nationwide Children’s Hospital
Update in Pediatric Asthma

• What’s new for chronic management
• What’s new for acute care
• What’s new for those pesky “wheezing” infant/toddlers

Case: 7 year old with poor asthma control

• You started Jacob on low dose ICS therapy last month
• He’s still having problems
• Mom (and pharmacy fill rates) vouch for good compliance
Case: 7 year old with poor asthma control

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What are your options?

Poor Control in a Compliant Patient – Check Inhaler Technique

- Standard: Spacer Use with HFA Inhaler
- New: Consider Breath Actuated Inhaler?
  - Now with multiple drug options
  - Pitfalls?
  - Age limits?
Poor Control in Compliant Patient – Increasing ICS Step-Up Option

• Potential for height growth suppression by ICS therapy remains a uniquely pediatric concern
  • Cochrane Review 2014 regarding ICS growth effects in prepubescent children
  • Small but significant decrease in growth velocity noted in those using low-medium dosed versus low-dose ICS
Poor Control in Compliant Patient – Adding Montelukast Option

- Montelukast and neuropsychiatric reactions
- European Respiratory Journal 2017 published study of children starting montelukast in “real-life”
- >10% stopped medication due to issues such as irritability, aggressiveness or sleep disturbances
### Poor Control in Compliant Patient – Medication Step-Up Options

<table>
<thead>
<tr>
<th>Option</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICS/LABA products no longer carry Black Box warning</strong></td>
<td>IC/LABA products are approved down to age 6 years&lt;br&gt;Especially effective for reducing day to day symptoms</td>
</tr>
<tr>
<td><strong>Add-on LAMA therapy for asthma control now FDA approved for ages 6 years and older</strong></td>
<td>Consider in those failing IC/LABA or intolerant to LABA&lt;br&gt;Appears to work despite underlying asthma “type”</td>
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### Poor Control in Compliant Patient – Medication Step-Up Options

<table>
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<tr>
<td><strong>Allergen immunotherapy</strong></td>
<td>Option when asthma is inadequately controlled despite standard medications and allergen avoidance&lt;br&gt;Single aeroallergen therapy to mite or pollen most helpful – efficacy of allergen mixes less clear</td>
</tr>
<tr>
<td><strong>Biologic therapies</strong></td>
<td>Omiluzimab (age 6 and older)&lt;br&gt;Mepolizumab (age 12 and older)&lt;br&gt;Benralizumab (age 12 and older)</td>
</tr>
</tbody>
</table>

These therapies warrant specialist referrals.
What about Fraction of Exhaled Nitrous Oxide (FeNo) Testing?

- Asthma diagnosis and medication adjustment traditionally hinges on symptoms/signs & spirometry
- FeNo (inflammatory marker elevated in allergic asthma) increasingly used as additional tool

So What is FeNO?

- Nitric oxide is produced by the airway epithelium of bronchial wall
- Production increases in eosinophilic airway inflammation, and can be measured in exhaled air
- In children, levels defined as:
  - Low <20 ppb
  - Intermediate 20-35 ppb
  - High >35 ppb
- Elevation suggests eosinophilic airway disease, and predicts likely corticosteroid responsiveness
### What role does FeNO have in Pediatric asthma management?

#### Issues:
- Eosinophilic inflammation is seen in most, but not all childhood asthma
- Levels can also be elevated in atopy & allergic rhinitis
- Levels are suppressed by ICS therapy

#### For Diagnosis:
- Potentially helpful if asthma diagnosis is unclear following initial history, exam & spirometry testing
- Need to remember low values may be due to non-eosinophilic disease

#### For Management:
- Elevation suggests ICS non-compliance (or oncoming flare)
- Medication adjustment per FeNO in addition to usual strategies has limited impact on outcomes
Case: 9 year old with acute exacerbation

- 2 days into a cold, Robert woke with cough and wheeze that didn’t respond to albuterol
- His family brought him to the Emergency Department

What’s new in acute asthma management?

Same key drugs – different delivery options

**Short Acting Beta-agonists (SABA)**
- Can be delivered by nebulizer OR MDI/Spacer
- 2.5 mg albuterol by nebulizer typically matched to 4-8 puffs via valved holding chamber

**Systemic Corticosteroids**
- Timing is important – goal < 60 minutes from presentation
- Dexamethasone (1 or 2 doses, 0-3-0.6 mg/kg) may be as effective as prednisone (3-5 days, 1-2 mg/kg/day)
### Additional Therapies

- **Oxygen** (of course)
- **Ipratropium**
  - Helpful when added to albuterol *in the ED*
  - Dosing 250-500 µg by nebulizer OR 2-3 puffs of 17µg/puff inhaler up to 3 doses
- **Magnesium (IV)**
  - Considered if suboptimal response to albuterol/ipratropium plus systemic steroids
  - Smooth muscle relaxant, reduces hospitalization rates

### For those with persistent severe air exchange difficulty

- **Heliox**
- **BiPAP**
- **Continuous albuterol**
- **Rarely**
  - IV beta-agonists (discouraged due to side effects)
  - IV theophylline (discouraged due to side effects)
  - Intubation (High risk for complications)
  - Extra-Corporeal Membrane Oxygenation (ECMO)
Role of Follow-up

- Confirm improvement
- Critically, adjust plan to help avoid repeat event
  - Review adherence
  - Start or adjust controller therapy*
  - Construct an asthma action plan
  - Make referrals if needed

* Increasingly, controller refills or changes may occur in ED setting as well

Case: 12 month old with persistent cough and noisy breathing

- Otherwise healthy child developed bronchiolitis at age 7 months, and has remained symptomatic ever since
- Chronic cough, “wheeze” with rattling quality
- Albuterol helps somewhat. Steroids “don’t do anything.”

What’s new for noisy infant/toddlers?
The Special Challenges of Wheezing Infants and Toddlers

• Recurrently wheezing infants and toddlers is challenging to manage
• Even in infants with proven airway reactivity, eosinophilic inflammation typically isn’t present
• Family history, personal signs of atopy increase likelihood of asthma by school age

When to worry it’s NOT just episodic airway inflammation/“Asthma”

• Symptoms present from birth
• Poor growth
• Stridor component
• Failure to respond to asthma medications
• Recurrent severe episodes
• Symptoms rarely resolve
### Potential Causes of Unremitting Symptoms

- Large airway narrowing or obstruction
  - Vascular rings
  - Tracheal stenosis or malacia
  - Foreign body
  - Mediastinal masses
- Small airway infection or secretions
  - Aspiration
  - Cystic fibrosis
  - Primary Ciliary Dyskinesia
  - *Protracted Bacterial Bronchitis*

### Protracted (Persistent) Bacterial Bronchitis: Presentation

- Increasing recognized cause of persistent (over 4 weeks) wet/productive sounding cough
- In toddlers/older infants may also present with parent reported “wheeze” with wet/rattling quality
- May be semi-responsive to albuterol, and mistaken for “asthma”
- PBB patients otherwise appear well with normal growth & development, lack of systemic symptoms
Protracted Bacterial Bronchitis: Test Results

- CXR:
  - Normal to nonspecific airway changes
- Bronchoscopy/BAL findings*:
  - Frequently, some degree of airway malacia
  - Marked increase in neutrophils
  - Bacteria: H. influenza, S. pneumoniae, M. catarrhalis (Often in combination)

Protracted Bacterial Bronchitis: Diagnosis and Management

- Diagnosis can be based on symptoms – and response to trial of antibiotic therapy
- If symptoms improve within 2 weeks, complete 4-6 weeks of continuous therapy
- Bronchoscopy & BAL are not necessary if presentation and therapy response are straightforward
- Consider specialist referral if no response to initial antibiotics, or rapid recurrence off therapy
• New agents to complement ICS therapy
• New delivery device/inhaler options
• Evolving use of FeNO in outpatient management
• Oral steroid options for acute management
• New differential possibility – protracted bacterial bronchitis – for young patients with chronic "rattling" and cough