WHAT’S NEW WITH ASTHMA?

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OUTLINE
1. Review of pathophysiology and epidemiology of asthma
2. List medications used in the treatment of asthma
3. Discuss asthma management based on accepted guidelines
4. Introduce novel treatments for asthma

Asthma
- 22 million Americans affected
- Burden of poorly controlled asthma is great
  - Lost school
  - Lost work
  - Less quality of life
  - Avoidable ER visits, hospitalizations, and deaths
- Complex disorder characterized variable and recurring symptoms
- Reversible airflow obstruction, bronchial hyperresponsiveness, and inflammation
Reversible Airflow Obstruction

- Airway hyperresponsiveness
- Airway edema
  - Mucus hypersecretion, formation of inspissated mucus plugs further limit airflow
- Bronchoconstriction
  - Exposure to a variety of stimuli, including allergens or irritants
  - Airways remodeling with increased smooth muscle mass

Asthma Diagnosis

- Detailed history and physical exam
  - Absence of symptoms at time of exam does not exclude diagnosis
- Spirometry with pre/post bronchodilator
  - Reversibility: ↑ FEV₁ or FVC of ≥ 12% predicted and 200 cc
  - Do not use peak flow measurements for DX
  - Normal spirometry does not exclude diagnosis
- PRN additional studies
**Asthma Diagnosis**
- PRN additional studies
  - PFTs (? emphysema, restriction, VCD, central obstruction)
  - DLCO differentiates emphysema from asthma
  - Methacholine bronchoprovocation if normal FEV,
    - Negative test excludes asthma
  - CXR
  - Allergy testing
  - No biomarkers (?FeNO)

**Peak Flow Measurement**
- Not reliable to assess severity "classification": use FEV,
- For Monitoring
  - Symptom-based monitoring is as good as PEF
  - Moderate or severe asthmatics
  - Hx of severe exacerbations

**Blood Gases in Asthma**
- If:
  - Suspect hypoventilation
  - Severe stress or FEV1 or PEF ≤ 25% of predicted after initial Rx
- Increased A-a gradient
- +/- ↓ PO2 with ↑ PCO2 and respiratory alkalosis = expected
  - ABGs that look normal during an attack signal severe obstruction \\
    & respiratory muscle fatigue → intubate
Asthma Medications

- **SABAs**
- **LABAs**
- **Steroids: inhaled and oral**
- **Anticholinergics**
- **Mast cell stabilizers**
- **Methylxanthines**
- **LTRAs**

### Inhaled Steroids
- Flunisolide
- Fluticasone
- Mometasone
- Budesonide
- Beclomethasone
- Triamcinolone
  - **LABAs**
  - **SABAs**
  - **Anticholinergics**
  - **Mast Cell Stabilizers**
  - **Methylxanthines**

### Anticholinergics
- Ipratropium
- Tiotropium
- Albuterol
- Levalbuterol
- Pirbuterol

### Mast Cell Stabilizers
- Cromolyn
- Nedocromil

### Methylxanthines
- Theophylline
- Leukotriene modifiers
  - Montelukast
  - Zafirlukast
- Zileuton
**SABAs**
- **Albuterol** = drug of choice for acute asthma symptoms
- Drug of choice for preventing EIB
- Not for daily use (except in EIB)
- Goal of "control" = < 2x/week use
- If using SABAs > 2x/week, intensify treatment

**LABAs**
- Adjunct to ICS for long-term control of symptoms; preferred treatment in adults
- Never, Ever, Ever, Never, Ever for monotherapy!
  - Boxed warning for increased risk of death when used without ICS for treatment of asthma
- Not for acute symptoms or exacerbations
- May be used to prevent EIB but not daily

**Inhaled Corticosteroids**
- Most effective Rx for mild, mod, or severe persistent
- Well-tolerated and safe
- Use lowest dose that maintains control
- Add LABAs to low- or medium-dose ICS before ↑ strength of ICS
Oral Corticosteroids

- Chronic = Only most severe, difficult-to-control asthma

- Acute exacerbations
  - Definite indication: PEF < 79% predicted/personal best after SABA x 2

Anticholinergics

- Multiple doses, + SABAs, for ER treatment of moderate/severe asthma

- Single agent only if intolerant of beta-agonists

- Not for hospitalized exacerbations

- Currently, do not use long-acting anticholinergics (tiotropium) in asthma
“Alternative” Therapies
- For mild asthma and not “preferred”
  - Mast cell stabilizers
  - Methylxanthines
    - Watch for drug interactions and toxicity
  - Leukotriene modifiers
    - Unmasking of Churg-Strauss vasculitis
- For severe asthma
  - Omalizumab
    (Step Six medication)

MANAGEMENT

Asthma NAEPP Guidelines
- National Asthma Education and Prevention Program
- First guidelines in 1992, updated in 1997 and 2002
- Last Updated in 2007
- New focus for assessing control, impairment and risk
- Stepwise approach to treatment
- Focus on patient education
- Use worse variable rule
NAEPP 2007

- Severity
  - Intrinsic intensity of the disease process
  - Most easily measured in patients not on treatment
  - Can be measured after control is achieved by the step of care required to maintain control
- Control
  - Degree to which the manifestations of asthma are minimized by therapeutic intervention
- Risk
  - Likelihood of either asthma exacerbations, progressive decline in lung function, or risk of adverse effects of treatment

Acute Exacerbations

- Home management based on Action Plan
- Emergency Department
- Hospital Admission
Try to understand the basic stepwise concepts here, and you won’t need to memorize this whole table.

Start: SABA → ICS → ICS + LABA → increase dose ICS + LABA
Exercise-Induced Bronchospasm

- Bronchodilation with exercise → bronchoconstriction after → resolution in 15–60 minutes
- Diagnosis: PFTs.
  - Exclude asthma and variable obstruction caused by vocal cord dysfunction
- Goal: Participate in whatever activity patient chooses without symptoms
  - Intermittent: SABA 10 minutes before exercise
  - Daily use: Leukotriene modifier or ICS, not LABA!

Vocal Cord Dysfunction

- Ages 20–40 years, ♀ > ♂
- Paradoxical VC adduction during inspiration
- ? Fumes, cold air, exercise
- Episodic dyspnea & stridor that may be confused with asthma/EIB
- Illness Script: Athlete who presents with exercise-related breathlessness & does not respond to Rx for EIB
- Dx: Flow-volume loop → variable extrathoracic obstruction (flattening of inspiratory curve)

AR Question 1
What are you supposed to do with a peak flow meter?

A. Use the results to diagnose asthma.
B. Wildly wave it in your patient's face and say, "Do you want to end up intubated?"
C. Use it for monitoring of control of asthma.
What are you supposed to do with a peak flow meter?

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AR Question 2
An 18-year-old female to the ED complaining, “Can’t breathe.”

Diaphoretic, 140/90, HR 128, RR 30
“Inspiratory Fall in Blood Pressure”
Leaning forward, accessory muscles
Hyperresonance
Diffuse wheezes
ABG on room air:
\[ \text{pH} 7.39 \quad \text{pCO}_2 45 \text{ mmHg} \]
\[ \text{pO}_2 60 \text{ mmHg} \]

Which of the following is the most appropriate next step in management?

A. Magnesium sulfate IV
B. Noninvasive mask ventilation
C. 40% FiO\(_2\) by face mask
D. Antibiotic therapy
E. Intubation and mechanical ventilation
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AR Question 3

A 16-year-old male:
Exertional wheezing and dyspnea at height of running for track
Sxs remain several hours after activity
Tried friend’s albuterol inhaler 10 minutes before run, but not sure if helps

No tobacco use
PMH: Prolonged ICU stay for Guillain-Barré at age 12
Normal physical exam

Which of the following is the most appropriate course of action?

A. Prescribe a short-acting beta-agonist before exercise.
B. Prescribe cromolyn sodium as prophylaxis for exercise-induced asthma.
C. Perform PFTs and assess the flow-volume loop.
D. Perform a methacholine bronchoprovocation test to diagnose asthma.
E. Perform fluoroscopy of the diaphragm to document residual paralysis.
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AR Question 4
An adherent 26-year-old female for routine F/U.
Dx: Asthma, age 16; ICU x 1 at age 17, no ventilator
ROS: Daily wheezing requiring albuterol, nocturnal cough 3x/week
Meds: Beclomethasone 80 mcg bid, albuterol prn
PE:
Normal vital signs
No JVD
Lungs with symmetric expansion, resonant to percussion, clear to auscultation

Which of the following is the most appropriate next step in patient care?
A. Add ipratropium bromide bid.
B. Add salmeterol bid.
C. Perform a polysomnogram.
D. Add theophylline.
E. Add montelukast daily.
Which of the following is the most appropriate next step in patient care?

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B. Add salmeterol bid.
C. Perform a polysomnogram.
D. Add theophylline.
E. Add montelukast daily.

NOVEL TREATMENTS

- Magnesium sulfate
- High-dose inhaled steroids
- Anticholinergics
- IV LTRAs
- Inhaled heparin
- Heliox
Bronchial Thermoplasty

- Bronchoscopic treatment aimed at reversing smooth muscle hypertrophy
- FDA approved 2010
- Applies thermal energy (radiofrequency ablation) directly to bronchial walls
  - 65°C delivered for 10 seconds per activation
  - Reduced central airway smooth muscle mass
  - Reduced airway hyperresponsiveness

Bronchial Thermoplasty

- Outpatient procedure performed over 3 treatment sessions, 3 weeks apart by a trained pulmonologist
- Complimentary treatment
  - Not a cure
  - No known effects on airways inflammation
    - ICS, LABA's, etc. must still be continued
Bronchial Thermoplasty

- **Patient selection**
  - FDA indication: Treatment of severe persistent asthma in patients ≥ 18yo whose asthma is not controlled with high dose ICS and LABA's

- **Contraindications**
  - Pacemakers, ICD's, other implantable electronic devices
  - Anticoagulation/anti-platelet therapy
  - Unable to safely undergo bronchoscopy
  - Previously treated with BT

Clinical Trials

- **Research in Severe Asthma (RISA) Trial**
- **Asthma Intervention Research (AIR) 2 Trial**
- **AIR 2 post-approval 5 year data**

RISA Trial

- **Multicenter, RCT**
  - 8 sights, 3 countries

- **Primary objective:**
  - Determine safety of Bronchial Thermoplasty (BT) with the Alair™ System in patients with symptomatic, severe asthma

- **Secondary objectives:**
  - Effect of BT on asthma symptoms and daily medication requirements

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RISA Results

- 32 subjects
  - 15 BT
  - 17 Control
- Safety assessment (Primary objective)
  - Increased adverse respiratory events in BT group in treatment period
    - wheeze, cough, chest discomfort, dyspnea, productive cough, discolored sputum
  - No difference in post-treatment period

AIR 2 Study

- Randomized, double-blind, sham-controlled
- 30 U.S. sights
- Study subjects:
  - Adults (18-65 yo)
  - High dose ICS and LABA
  - Leukotriene modifiers, Omalizumab, and OCS<10 mg/day were allowed
AIR2 Results

- 297 patients randomized in 2:1 ratio
- AQLQ
  - Mean change in AQLQ was greater in BT group
    - 1.35 vs. 1.16 (PPS=96%)
    - Larger % had a clinically relevant change
      - 79% vs 54% (PPS=99.6%)
- Exacerbations
  - Reduced excac in BT group (0.48 vs 0.70 excac/pt/year, PPS=95.5%)
  - Fewer work days lost
  - No statistically different change in AM PEF, symptom free days, or rescue medication use.

AIR2 Healthcare Utilization

AIR2 Five Years Later

Reduction in Severe exacerbations persisted through 5 years, with average reduction of 44%
AIR2 Five Years Later

Reduction in ED visits was maintained for 5 years with average reduction of 78%.

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Bronchial Thermoplasty

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<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td>Improved QOL</td>
<td>Pathophysiology not well understood</td>
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<tr>
<td>Fewer days lost from work, school, other activities</td>
<td>Long term effects unknown</td>
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<tr>
<td>Fewer exacerbations</td>
<td>Treatment related exacerbations common</td>
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<td>5-yr reduction in severe exacerbations requiring systemic corticosteroids</td>
<td>Blinding concerns in RCT's</td>
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<tr>
<td>Fewer ED visits</td>
<td>Concern over widespread use without appropriate comprehensive asthma care</td>
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<tr>
<td>No decline in lung function</td>
<td>Placebo effect of AIR2</td>
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<td>Safety profile</td>
<td>Insurance approval</td>
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<td>Healthcare cost savings???</td>
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SUMMARY