UPDATES IN ASTHMA MANAGEMENT
WHAT THE PRIMARY CARE PA NEEDS TO KNOW

Amanda Hess, MMS, PA-C
President-Elect, AAPA-AAI
Arizona Asthma and Allergy Institute
Scottsdale, AZ
Financial Disclosures

- Advanced Practiced Advisory Board for Circassia
Learning Objectives

1. Briefly review epidemiology, pathophysiology and risk factors for asthma
2. Review diagnosis and spirometry findings in asthma.
3. Review step-therapy guidelines for management of asthma
4. Discuss differential diagnosis of asthma.
5. Discuss what and how the primary care provider can identify these patients in order for specialist referral.
What is asthma?

- A heterogeneous disease usually characterized by chronic airway inflammation
- Defined by history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation
  - Symptoms associated with variable expiratory airflow
    - Bronchoconstriction
    - Airway wall thickening
    - Increased mucous
Epidemiology

- One of the most common chronic diseases worldwide
- Prevalence increasing in many countries, especially in children
- Can be controlled, but not cured
Clinical Presentation

- Usually more than one type of symptom:
  - Wheeze, shortness of breath, cough, chest tightness
- Symptoms vary over time and in intensity
  - "Episodic"
- Symptoms often worse at night or early in the morning
- Triggered by viral URI, exercise, allergen exposure, weather changes, laughter, irritants, smoke or strong smells
Clinical Presentation

- PE often normal
- Most frequent finding: Wheezing
  - However, wheezing also found in other conditions:
    - Respiratory infections, COPD, upper airway dysfunction, bronchial obstruction, foreign body
  - Wheezing can be ABSENT during severe exacerbations
    - “Silent chest”
Risk Factors

- Presence of atopic dermatitis or allergic rhinitis
- Parents or siblings with asthma
- Overweight/obesity
- Smoker or secondhand smoke exposure
- Exposure to pollution or fumes
- Maternal smoking during pregnancy
- Urban settings
- Frequent exposure to viral infections
- In childhood, more common in boys
  - M=F by age 20
  - F > M by age 40
DDX: “Asthma Mimickers”

- Vocal cord dysfunction
- Gastroesophageal reflux disease
- Allergic rhinitis
- Coexisting COPD
- Restrictive lung disease
- Central airway obstruction
- Cystic fibrosis
- Foreign body/aspiration
- Bronchiolitis
- Laryngotracheomalacia
- Heart disease
- Pulmonary embolism
- Tumors
Diagnosis is less likely asthma if...

- Isolated cough and no other symptoms
- Chronic sputum production
- Shortness of breath with associated dizziness
- Chest pain
- Exercise-induced dyspnea with stridor
Diagnosis of Asthma

- Confirmed presence of airflow limitation on pulmonary function testing
  - Reduced FEV1/FVC
    - Normally ≥0.75 in adults, >0.90 in children
- Bronchodilator reversibility
  - Adults ≥12% and ≥200mL improvement in FEV1
  - Children ≥12% predicted
- Significant improvement in FEV1 or PEF after 4 weeks of controller use
- If initial testing negative:
  - Repeat when symptomatic or off bronchodilators
  - Refer for additional tests (full PFT, methacholine challenge)
Lung volumes and capacities depicted on a volume-time spirogram. The most important values are the forced vital capacity (FVC), the forced expiratory volume in 1 second (FEV₁), and the FEV₁/FVC ratio. Spirometry cannot measure the residual volume or the total lung capacity.
Spirometry and Volume-Time Curve

**FIGURE 2.** Volume-time curve and flow-volume curve

**Spirometry in Obstructive Lung Disease**

### TABLE 2

#### Obstructive and restrictive patterns

<table>
<thead>
<tr>
<th>MEASUREMENT</th>
<th>OBSTRUCTIVE PATTERN</th>
<th>RESTRICTIVE PATTERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced vital capacity (FVC)</td>
<td>Decreased or normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 second (FEV₁)</td>
<td>Decreased</td>
<td>Decreased or normal</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Total lung capacity (TLC)</td>
<td>Normal or increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

#### Table 2: Lower Limit of Normal, Pre-Bronchodilator, % of Predicted Value, Post-Bronchodilator, % Change

<table>
<thead>
<tr>
<th></th>
<th>LOWER LIMIT OF NORMAL</th>
<th>PRE-BRONCHO-DILATOR</th>
<th>% OF PREDICTED VALUE</th>
<th>POST-BRONCHO-DILATOR</th>
<th>% CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced vital capacity (FVC)</td>
<td>2.24 L</td>
<td>2.42 L</td>
<td>83%</td>
<td>2.72 L</td>
<td>12%</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 second (FEV₁)</td>
<td>1.86 L</td>
<td>1.52 L</td>
<td>63%</td>
<td>2.05 L</td>
<td>34%</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>73.4%</td>
<td>58.2%</td>
<td>75.3%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Forced expiratory time</td>
<td>11.2 sec</td>
<td>10.7 sec</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other biomarkers

- Fractional Exhaled Nitric Oxide (FENO)
- Serum eosinophil counts
- Total serum IgE levels
Treatment goals in asthma

- Long term goals:
  - Symptom control with normal activity levels
  - Reduce risk of future exacerbations
  - Minimize potential for fixed airway obstruction
  - Minimize medication side-effects

- Patient-Provider relationship:
  - “What are YOUR goals?”
  - Good communication
  - Personal and cultural preferences
  - Medication availability and cost

- Reinforcement
  - Inhaler technique, adherence, asthma action plan
Non-Pharmacological Intervention

- Avoiding tobacco smoke
- Physical activity
- Occupational changes
- Avoid medications that can worsen asthma
  - NSAIDs, Beta-blockers
- Allergen avoidance
- Immunotherapy
Figure 2 GINA guidelines for management of asthma.
Notes: Note the recommendation to add tiotropium in steps 4 and 5, after maximizing other medical therapy. Reproduced with permission from Global Initiative for Asthma (GINA) Teaching Slide Set, 2015 Update (Slide 63). For children 6–11 years, theophylline is not recommended, and preferred Step 3 is medium-dose ICS. For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy, Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.
Abbreviations: BDP, beclomethasone dipropionate; BUD, budesonide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β-2 agonist; theoph, theophylline; IgE, Immunoglobulin E; OCS, oral corticosteroid.
Step 1: Mild Intermittent Asthma

- As-needed short-acting beta$_2$-agonist (SABA)
  - Albuterol (Proair, Ventolin, Proventil) or Levalbuterol (Xopenex)

- For patients with infrequent symptoms, short duration

- For exercise-induced bronchospasm

- Other options: Adding low dose inhaled corticosteroid (ICS) for patients at risk of exacerbations

When to start controller therapy or when to step up therapy?

- Asthma symptoms more than 2x per month
- Waking due to asthma more than 1x per month
- 2 or more exacerbations requiring oral steroids in the past year

If initial presentation is with an asthma exacerbation:
- Short oral steroid burst and start regular controller treatment

Step 2: Mild Persistent Asthma

- Regular low dose ICS with as-needed SABA
- Other options:
  - Leukotriene receptor antagonists (LTRA) with as-needed SABA
    - Less effective than low-dose ICS
    - Consider in some patients with asthma and allergic rhinitis
    - Exercise-induced symptoms with allergic rhinitis
    - Unable to use ICS
  - Intermittent ICS with as-needed SABA for purely seasonal allergic asthma
    - Start ICS when symptoms start and continue 3-4 weeks after allergy season
  - Consider allergen immunotherapy

Global Strategy for Asthma Management and Prevention
Update 2017. www.ginaasthma.org
Before considering next step:

- Check inhaler technique
- Discuss adherence
  - ICS are least-adhered medication. EVER!
  - Consider once-daily dosing
- Confirm diagnosis
  - Consider DDx!
Step 3: Moderate Persistent Asthma

- Low dose ICS/LABA plus as-needed SABA
- Other options:
  - Medium dose ICS
    - 0-4 year olds
  - Low dose ICS + LRTA
  - Low dose ICS + Theophylline

- Adding LABA reduces symptoms and exacerbations, increases lung function, allows for lower ICS dose
Step 4: Severe Persistent Asthma

- Medium to high dose ICS/LABA with as-needed SABA
- Children: Refer to specialist!
- Other options:
  - Add-on therapy with LTRA or Theophylline
  - Tiotropium as add-on therapy for >6 years old
  - Consider immunotherapy
  - Consider biologics

Stepping-Up Therapy

Stepping Up From GINA Step 2 to Step 3 - Patient Profile:
Symptomatic* ≥2 months or 2 or more exacerbations requiring OCS in past year, despite preferred treatment for mild, persistent asthma (ie, low-dose ICS monotherapy) and optimal adherence**

- Switch to low-dose ICS/LABA
- OR increase ICS dose
- OR add LTRA or SRT

3-month therapeutic trial with reassessment at 2-6 weeks

Stepping Up From GINA Step 3 to Step 4 - Patient Profile:
Symptomatic* ≥2 months or 2 or more exacerbations requiring OCS in past year, despite using low dose ICS/LABA (OR medium-dose ICS, ICS and SRT, OR ICS and LTRA) and optimal adherence**

Refer to asthma specialist

Continue to optimize medication:
- Increase to medium, then high dose ICS/LABA, AND/OR
- Add tiotropium soft mist inhaler, AND/OR
- Add small-particle ICS (or use small-particle ICS/LABA)

3-month therapeutic trial with reassessment at 2-6 weeks

**Step Therapy: Updated GINA Guidelines**

**Preferred controller choice**

- **Step 1**: Consider low-dose ICS
  - Leukotriene receptor antagonists (LTRA)
  - Low-dose theophylline

**Other controller options**

- **Step 2**: Low-dose ICS

**Reliever**

- **Step 1**: As-needed short-acting beta₂-agonist (SABA)

**Step 2**

- **Step 3**: Med/high-dose ICS
  - Med/high-dose ICS + LTRA
  - Med/high-dose ICS + LTRA or theophylline

**Step 4**

- **Step 4**: Add tiotropium
  - Add tiotropium or low-dose ICS/formoterol

**Step 5**

- **Step 5**: Refer for add-on treatment eg anti-IgE

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**Figure 2** GINA guidelines for management of asthma.

**Notes:** Note the recommendation to add tiotropium in steps 4 and 5, after maximizing other medical therapy. Reproduced with permission from Global Initiative for Asthma (GINA) Teaching Slide Set, 2015 Update (Slide 63). For children 6–11 years, theophylline is not recommended, and preferred Step 3 is medium-dose ICS. For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy. Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.

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Step 5: Severe Persistent Asthma

- Refer to specialty care
- Add-on LAMA
  - Tiotropium approved for patients >6 years old
- Low dose oral corticosteroids
- Consider biologics
  - Anti-IgE (Omalizumab/Xolair) for severe allergic asthma
  - Anti-IL5 (Mepolizumab/Nucala, Reslizumab/Cinqair)
  - Anti-IL5 receptor (Benralizumab/Fasenra)

Global Strategy for Asthma Management and Prevention
Update 2017. www.ginaasthma.org
Stepping Up Therapy:

Stepping Up From GINA Step 4 to Step 5 - Patient Profile:
Difficult-to-treat asthma: Symptomatic* ≥ 2 months or 2 or more exacerbations requiring OCS in past year, despite using high doses of anti-inflammatory and bronchodilator medications and optimal adherence**

Consider treatment targeted to the patient’s phenotype or characteristics

Asthma specialist care required

Other treatment options:

- Neutrophilic asthma
  - Macrolide antibiotics + Corticosteroids
- Bronchial thermoplasty

Treating Exacerbations

- Assess patient
  - Start SABA +/- Oxygen
  - Assess dyspnea
  - Rule out anaphylaxis
  - Risk for asthma related death?
- Consider alternative causes
  - Heart failure, PE, etc
- Arrange transfer to ED if signs of severe or life-threatening exacerbation
  - Immediately give Duoneb, Oxygen, Steroids
Treating exacerbations

- Review response
  - Monitor patient closely and frequently
  - Decide about need for hospitalization

- Before discharge, arrange ongoing treatment
  - Increased controller doses for 2-4 weeks
  - Arrange early follow-up within 2-7 days

Managing exacerbations in primary care

**PRIMARY CARE**
Patient presents with acute or sub-acute asthma exacerbation

**ASSESS the PATIENT**

- Is it asthma?
- Risk factors for asthma-related death?
- Severity of exacerbation?

**MILD or MODERATE**
- Talks in phrases, prefers sitting to lying, not agitated
- Respiratory rate increased
- Accessory muscles not used
- Pulse rate 100–120 bpm
- O₂ saturation (on air) 90–95%
- PEF >50% predicted or best

**SEVERE**
- Talks in words, sits hunched forwards, agitated
- Respiratory rate >30/min
- Accessory muscles in use
- Pulse rate >120 bpm
- O₂ saturation (on air) <90%
- PEF ≤50% predicted or best

**LIFE-THREATENING**
- Drowsy, confused or silent chest

**START TREATMENT**
- SABA 4–10 puffs by pMDI + spacer, repeat every 20 minutes for 1 hour
- Prednisolone: adults 1 mg/kg, max. 50 mg, children 1–2 mg/kg, max. 40 mg
- Controlled oxygen (if available), target saturation 93–95% (children: 94–98%)

**CONTINUE TREATMENT** with SABA as needed

**ASSESS RESPONSE AT 1 HOUR (or earlier)**

**WORSENING**

**TRANSFER TO ACUTE CARE FACILITY**
- While waiting: give SABA, O₂, systemic corticosteroid

**ASSESS FOR DISCHARGE**
- Symptoms improved, not needing SABA
- PEF improving, and >60–80% of personal best or predicted
- Oxygen saturation >94% room air
- Resources at home adequate

**ARRANGE at DISCHARGE**
- Reliever: continue as needed
- Controller: start, or step up. Check inhaler technique, adherence
- Prednisolone: continue, usually for 5–7 days (3–5 days for children)
- Follow up: within 2–7 days

**FOLLOW UP**
- Reliever: reduce to as-needed
- Controller: continue higher dose for short term (1–2 weeks) or long term (3 months), depending on background to exacerbation
- Risk factors: check and correct modifiable risk factors that may have contributed to exacerbation, including inhaler technique and adherence
- Action plan: Is it understood? Was it used appropriately? Does it need modification?
Risk factors for asthma-related death

- History of near-fatal asthma requiring intubation and ventilation
- Hospitalization or ED care in the last 12 months
- Poor compliance with ICS
- Oral corticosteroid-dependent
- Over-use of SABA
- History of psychiatric disease
- Presence of IgE-mediated food allergy

These patients need to be seen more frequently for follow up!
Asthma Action Plans

- Should include:
  - Usual medications
  - When and how to increase meds
  - When to start OCS
  - How to access medical care if no improvement
- Can be based on symptoms or PEF
- Medication changes:
  - ICS: Double dose
  - Maintenance ICS/formoterol: Quadruple dose
  - Maintenance ICS/salmeterol: Step up to higher dose or add more ICS

After an exacerbation

- Close follow up in 2-7 days
- Exacerbation = failure in chronic asthma care and management needs to be re-assessed
- Review:
  - What patient feels caused the exacerbation
  - Modifiable risk factors
  - Inhaler technique and purpose of medications
  - Review/revise written asthma action plans
Pathophysiology of Asthma
Anti-IgE: Xolair/Omalizumab

- Many asthmatics have some type of allergic sensitivity and increased serum total IgE levels

- IgE triggers release of inflammatory mediators and can cause increased asthma symptoms or exacerbations

- Increased serum IgE levels associated with more severe asthma

Anti-IgE: Xolair

- Prevents circulating IgE from triggering inflammatory cascade seen in allergic asthma
- Reduced exacerbation rates & asthma symptoms
- Improved quality of life
- Decreased controller use

Anti-IgE: Xolair
Anti-IgE: Xolair

- Evidence of allergic sensitization to perennial allergen and elevated IgE level (30-700 IU/mL)
- Dose is dependent on age, weight and pre-treatment IgE levels
  - Dose ranges from 150-375mg , q2 or q4 weeks
- Subcutaneous injection
- Usually well-tolerated
- Side effects:
  - Nasopharyngitis, headache, URI, sinusitis
  - Rare occurrence of anaphylaxis - monitor after injections (90-120 minutes)
  - Early trials showed possible increased malignancy rates, but several studies since then have not found this

Anti-IL-5: Nucala/Mepolizumab or Cinqair/Reslizumab

- Activation of IL-5 pathway in asthma recruits eosinophil production and development

- Eosinophils have long been associated with asthma
  - Airway injury
  - Airway hyper-responsiveness
  - Remodeling
  - Asthma severity

- Both Nucala and Cinqair target IL-5 pathway and eosinophils

Anti-IL-5: Nucala/Cinqair
Anti-IL-5: Nucala/Cinqair

- Improvement in eosinophil levels
- Reduced asthma exacerbation rates
- Improved quality of life
- Decreased oral and/or inhaled corticosteroid dose
- Cinqair did show improvement in FEV1 and FVC

Patients with severe persistent asthma who meet required threshold pre-treatment eosinophil levels (on CBC with differential)

**Nucala: ages 12+**
- Eosinophils: At least 150 cells/µL
- 100mg dose administered SQ q 4 weeks

**Cinqair: ages 18+**
- Eosinophils: At least 300 cells/µL
- 3mg/kg via IV infusion q 4 weeks

Tolerated well by patients
- Injection site reactions, headache, fatigue, pharyngitis
- Warning: Allergic reactions, Herpes Zoster infection, helminth infections
Anti-IL-5α: Fasenra/Benralizumab

- Specifically targets alpha-subunit of Anti-IL-5 receptor
- Depletes eosinophils more effectively
- Also induces apoptosis of basophils and other cells that are affected by IL-5
- Reduces asthma exacerbations (70% reduction over 1 year)
- Decreased steroid dose

Anti-IL-5α: Fasenra/Benralizumab

- Used in severe asthma with eosinophilic phenotype
  - No threshold eosinophil criteria

- Tolerated well, similar adverse effects as other anti-IL-5 therapy

- 30mg administered SQ every 4 weeks for first 3 doses, then every 8 weeks
  - More convenient dosing

Anti-IL-5α : Fasenra/Benralizumab
Other potential (future) therapies

- Dupixent/Dupilumab
  - Approved for treatment in moderate-to-severe asthma
  - Binds to IL-4 receptor alpha-subunit, but also blocks signaling from IL-13
  - Reduced exacerbation rates

- CRTH2 antagonist: Fevipirant
  - Blocks prostaglandin receptor 2, which drives inflammation

- Tyrosine kinase inhibitor: Imatinib
- Higher-affinity anti-IgE: Ligelizumab

Who should I refer to a specialist?

- Children requiring 2 or more controllers (Step 3-4)
  - ICS/LABA
  - ICS plus LRTA
- Patients with significant allergic rhinitis
  - Immunotherapy!
- Adults at step 5
  - Highly consider in adults at Step 4
- Any patient requiring 2 or more oral steroid bursts per year
- Consider in patients on therapy with recent severe exacerbation
- Patients not responding to typical asthma therapy
What can I do if I suspect a patient has severe asthma and may need a biologic?

- Order labs while waiting for specialty consult
  - CBC with differential
    - Best if off oral steroids
  - Total serum IgE
  - IgE panel for aeroallergens
    - “Valley of the Sun” or “Zone 16” or “Southwestern” panel
Thank You!

Any Questions?

Amanda Hess, MMS, PA-C
E-mail: a.hess@azsneeze.com
Twitter: @allergyPAC