Asthma Update 2014

Eric S. Papierniak, DO
Malcom Randall VAMC
Assistant Professor of Medicine
UF Div. of Pulmonary, Critical Care, and Sleep Medicine
Goals/Objectives

- Review of 2014 GINA guidelines
  - Significant changes/additions
  - Severe asthma and exacerbations
- Newer therapies
  - Omalizumab (Xolair)
  - Bronchial thermoplasty
  - Tiotropium (Spiriva)
- Other (time permitting)
  - Pregnancy
  - AERD
What’s truly “new” in asthma?

- Not much
- Vitamin D?
- Monoclonal antibodies?
- New inhalers?
  - Only one: ciclesonide (Alvesco)
    - Single agent ICS only
    - Some theoretical benefits
  - fluticasone/vilanterol (Breo)?
Abbreviations

- SABA: Short Acting Beta Agonist (albuterol)
- LABA: Long Acting Beta Agonist (salmeterol/formoterol)
- LTRA: LeukoTriene Receptor Antagonist
- ABPA: Allergic BronchoPulmonary Aspergillosis
Abbreviations

- AERD: Aspirin Exacerbated Respiratory Disease
- VCD: Vocal Cord Dysfunction
- ICS: Inhaled Corticosteroid
- EPR-3: Expert Panel Report #3
- GINA: Global INitiative for Asthma
- PEF: Peak Expiratory Flow
Abbreviations

- BT: Bronchial Thermoplasty
- ACOS: Asthma/COPD Overlap Syndrome
Epidemiology

- Asthma is reported to affect 8-11% of the US population
- Over 22 million people
- Annual treatment costs (adults): 18 billion dollars
- Total costs (incl. missed work/school) is likely double that
Epidemiology

- Getting worse
- Prevalence of asthma has increased by 25-75% every 10 years since 1960
- The relative prevalence of severe asthma has also increased
- Total hospitalizations have decreased but % intubated has increased
Epidemiology

- More bad news:
- 40% of patients need urgent care for exacerbation at least once a year
- US mortality rate from asthma actually increased from the 1970’s-1990’s (opposite trend in most other western countries)
Much of this can be attributed to socioeconomic factors as minorities and others in urban areas with lower income, education, and access to care have 2x (adults) to 3x (children) the morbidity and mortality.
Initial evaluation

- Establish/confirm the diagnosis of asthma
- Assess symptoms (and control)
- Identify precipitants/comorbidities that may aggravate asthma
- Classify asthma severity
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the 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.
Establish the diagnosis of asthma

- Episodic symptoms of airflow obstruction (i.e., wheezing, cough, chest tightness)
- Obstruction is at least partially reversible
- Alternative diagnoses are excluded
Establish the diagnosis of asthma

- Pulmonary Function Testing (PFT’s) are crucial for the diagnosis of asthma
- Simple spirometry with post-bronchodilator testing is adequate if COPD is not being considered in the differential
Patient with respiratory symptoms

Are the symptoms typical of asthma?

YES

Detailed history/examination for asthma

History/examination supports asthma diagnosis?

YES

Perform spirometry/PEF with reversibility test

Results support asthma diagnosis?

YES

Empiric treatment with ICS and prn SABA

Review response

Diagnostic testing within 1-3 months

Treat for ASTHMA

NO

Clinical urgency, and other diagnoses unlikely

Further history and tests for alternative diagnoses

Alternative diagnosis confirmed?

YES

Treat for alternative diagnosis

NO

Repeat on another occasion or arrange other tests

Confirms asthma diagnosis?

YES

Consider trial of treatment for most likely diagnosis, or refer for further investigations

NO

TREAT FOR ASTHMA

© Global Initiative for Asthma
Increased probability that symptoms are due to asthma if:

- More than one type of symptom (wheeze, shortness of breath, cough, chest tightness)
- Symptoms often worse at night or in the early morning
- Symptoms vary over time and in intensity
- Symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants such as car exhaust fumes, smoke, or strong smells

Decreased probability that symptoms are due to asthma if:

- Isolated cough with no other respiratory symptoms
- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling
- Chest pain
- Exercise-induced dyspnea with noisy inspiration (stridor)
Establish the diagnosis of asthma

- When to suspect it is not asthma?
  - Long-time smoker (COPD)
  - Older than 50 with no prior history
### STEP 2: SYNDROMIC DIAGNOSIS IN ADULTS

(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

<table>
<thead>
<tr>
<th>Feature: if present suggests -</th>
<th><strong>ASTHMA</strong></th>
<th><strong>COPD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>□ Before age 20 years</td>
<td>□ After age 40 years</td>
</tr>
<tr>
<td>Pattern of symptoms</td>
<td>□ Variation over minutes, hours or days</td>
<td>□ Persistent despite treatment</td>
</tr>
<tr>
<td></td>
<td>□ Worse during the night or early morning</td>
<td>□ Good and bad days but always daily symptoms and exertional dyspnea</td>
</tr>
<tr>
<td></td>
<td>□ Triggered by exercise, emotions including laughter, dust or exposure to allergens</td>
<td>□ Chronic cough &amp; sputum preceded onset of dyspnea, unrelated to triggers</td>
</tr>
<tr>
<td>Lung function</td>
<td>□ Record of variable airflow limitation (spirometry or peak flow)</td>
<td>□ Record of persistent airflow limitation (FEV₁/FVC &lt; 0.7 post-BD)</td>
</tr>
<tr>
<td>Lung function between symptoms</td>
<td>□ Normal</td>
<td>□ Abnormal</td>
</tr>
<tr>
<td>Past history or family history</td>
<td>□ Previous doctor diagnosis of asthma</td>
<td>□ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema</td>
</tr>
<tr>
<td></td>
<td>□ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)</td>
<td>□ Heavy exposure to risk factor: tobacco smoke, biomass fuels</td>
</tr>
<tr>
<td>Time course</td>
<td>□ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year</td>
<td>□ Symptoms slowly worsening over time (progressive course over years)</td>
</tr>
<tr>
<td></td>
<td>□ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks</td>
<td>□ Rapid-acting bronchodilator treatment provides only limited relief</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>□ Normal</td>
<td>□ Severe hyperinflation</td>
</tr>
</tbody>
</table>

**NOTE:** These features best distinguish between asthma and COPD. Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Asthma</th>
<th>Some features of asthma</th>
<th>Features of both</th>
<th>Some features of COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONFIDENCE IN DIAGNOSIS</strong></td>
<td>Asthma</td>
<td>Possible asthma</td>
<td>Could be ACOS</td>
<td>Possibly COPD</td>
<td>COPD</td>
</tr>
</tbody>
</table>
Establish the diagnosis of asthma

- When to suspect it is not asthma?
  - Long-time smoker (COPD)
  - Older than 50 with no prior history
  - Symptoms such as palpitations or syncope
  - Poor response to asthma treatment
Establish the diagnosis of asthma

- PFT’s sometimes WNL
- Reversibility criteria are somewhat controversial
- Methacholine challenge: Better negative predictive value?
- Other testing as needed to rule out alternate diagnoses (CXR, etc)
“All that wheezes is not asthma”

- Coined by Chevalier Jackson
- Laryngologist
  - Developed modern open tracheostomy techniques
  - Pioneer in the development of self-lighted endoscopes
  - A specialist in foreign body retrieval
Initial evaluation

- Identify and treat comorbidities that may aggravate asthma
  - GERD
  - Sinusitis
  - Vit. D deficiency
  - Allergies
  - OSA
Initial evaluation

- Identify and treat comorbidities that may aggravate asthma
  - GERD
    - Little evidence that treating silent GERD improves asthma control
  - Sinusitis
  - Vit D. Deficiency
  - Allergies
  - OSA
Initial evaluation

- Identify and treat comorbidities that may aggravate asthma
  - GERD
  - Sinusitis
    - Preferred therapy is first generation antihistamines and nasal steroids
  - Vit D. Deficiency
  - Allergies
  - OSA
Initial evaluation

- Identify and treat comorbidities that may aggravate asthma
  - GERD
  - Sinusitis
  - Vit D. Deficiency
    - Ineffective at reducing exacerbations vs placebo
  - Allergies
  - OSA
Initial evaluation

- Identify and treat comorbidities that may aggravate asthma
  - GERD
  - Sinusitis
  - Vit D. Deficiency
  - Allergies
    - Allergy shots have limited efficacy in asthma
  - OSA
Initial evaluation

- Diagnosis made
- Classify asthma severity (two domains)
  - Future risk (exacerbations)
  - Current impairment (symptoms/PFTs)
- May not respond to therapy in parallel
Risk factors for exacerbations include:

- Ever intubated for asthma
- Uncontrolled asthma symptoms
- Having ≥1 exacerbation in last 12 months
- Low FEV$_1$ (measure lung function at start of treatment, at 3-6 months to assess personal best, and periodically thereafter)
- Incorrect inhaler technique and/or poor adherence
- Smoking
- Obesity, pregnancy, blood eosinophilia

Risk factors for fixed airflow limitation include:

- No ICS treatment, smoking, occupational exposure, mucus hypersecretion, blood eosinophilia

Risk factors for medication side-effects include:

- Frequent oral steroids, high dose/potent ICS, P450 inhibitors
Classification of severity

- Classic categories of intermittent or mild/mod/severe persistent asthma were static, complex, and often inappropriately applied to patients on high intensity therapy.
- Could result in under-treatment or underestimation of the true severity of disease.
Classification of severity

- Severity classification is now based on level or intensity of therapy needed to control the individual patient’s asthma
Assessing asthma severity

How?
- Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations

When?
- Assess asthma severity after patient has been on controller treatment for several months
- Severity is not static – it may change over months or years, or as different treatments become available

Categories of asthma severity
- **Mild asthma**: well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
- **Moderate asthma**: well-controlled with Step 3 (low-dose ICS/LABA)
- **Severe asthma**: requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment
# Classifying Asthma Severity and Initiating Treatment in Youths ≥ 12 Years of Age and Adults

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications.

## Classification of Asthma Severity

### ≥ 12 years of age

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-19 yr</td>
<td></td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39 yr</td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59 yr</td>
<td></td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-80 yr</td>
<td></td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td></td>
<td>≤2 x/month</td>
<td>3-4 x/month</td>
<td>&gt;1 x/week but not nightly</td>
<td>Often 7x/week</td>
<td></td>
</tr>
<tr>
<td>Short-acting beta agonist use for symptom control (not prevention of EIB)</td>
<td></td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily, and not more than 1x on any day</td>
<td>Daily</td>
<td>Several times per day</td>
<td></td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td></td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
<td></td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td>● Normal FEV₁ between exacerbations</td>
<td>● FEV₁ &gt; 80% predicted</td>
<td>● FEV₁ &gt; 60% but &lt;80% predicted</td>
<td>● FEV₁ &gt; 60% predicted</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● FEV₁/FVC normal</td>
<td>● FEV₁/FVC reduced 5%</td>
<td>● FEV₁/FVC reduced &gt;5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td></td>
<td>0-1/year</td>
<td>&gt;2/year</td>
<td>Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV₁.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recommended Step for Initiating Treatment</strong></td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
<td>Step 4 or 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and consider short course of oral systemic corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FEV₁* - forced expiratory volume in one second; *FVC* - forced vital capacity
Classification of Severity

- Assigning severity in follow up based on response helps differentiate between truly “severe” vs “uncontrolled” asthma

- More on this later
How to distinguish between uncontrolled and severe asthma

1. **Watch patient using their inhaler. Discuss adherence and barriers to use**
   - Compare inhaler technique with a device-specific checklist, and correct errors; recheck frequently. Have an empathic discussion about barriers to adherence.

2. **Confirm the diagnosis of asthma**
   - If lung function normal during symptoms, consider halving ICS dose and repeating lung function after 2–3 weeks.

3. **Remove potential risk factors. Assess and manage comorbidities**
   - Check for risk factors or inducers such as smoking, beta-blockers, NSAIDs, allergen exposure. Check for comorbidities such as rhinitis, obesity, GERD, depression/anxiety.

4. **Consider treatment step-up**
   - Consider step up to next treatment level. Use shared decision-making, and balance potential benefits and risks.

5. **Refer to a specialist or severe asthma clinic**
   - If asthma still uncontrolled after 3–6 months on Step 4 treatment, refer for expert advice. Refer earlier if asthma symptoms severe, or doubts about diagnosis.
Stepwise approach to control asthma symptoms and reduce risk

### GINA 2014, Box 3-5

© Global Initiative for Asthma
<table>
<thead>
<tr>
<th>Level of control</th>
<th>Treatment action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>Maintain and find lowest controlled step</td>
</tr>
<tr>
<td>Partly controlled</td>
<td>Consider stepping up to gain control</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>Step up until controlled</td>
</tr>
<tr>
<td>Exacerbation</td>
<td>Treat as exacerbation</td>
</tr>
</tbody>
</table>

### Treatment steps

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma education</td>
<td>Environmental control</td>
<td><strong>As-needed rapid-acting ( \beta_2 )-agonist</strong></td>
<td><strong>As-needed rapid-acting ( \beta_2 )-agonist</strong></td>
<td><strong>Controller options</strong></td>
</tr>
<tr>
<td>As-needed rapid-acting ( \beta_2 )-agonist</td>
<td><strong>Controller options</strong></td>
<td><strong>Controller options</strong></td>
<td><strong>Controller options</strong></td>
<td><strong>Controller options</strong></td>
</tr>
<tr>
<td>Select one</td>
<td>Select one</td>
<td>Add one or more</td>
<td>Add one or both</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS</td>
<td>Low-dose ICS plus long-acting ( \beta_2 )-agonists</td>
<td>Medium- or high-dose ICS plus long-acting ( \beta_2 )-agonists</td>
<td>Oral glucocorticosteroid (lowest dose)</td>
<td></td>
</tr>
<tr>
<td>Leukotriene modifier*</td>
<td>Medium- or high-dose ICS</td>
<td>Leukotriene modifier</td>
<td>Anti-IgE treatment</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS plus long-acting ( \beta_2 )-agonists</td>
<td>Low-dose ICS plus leukotriene modifier</td>
<td>Sustained release theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS plus sustained release theophylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Stepwise approach for managing asthma in persons ≥ 12 years of age

### Intermittent Asthma
- Consult with asthma specialist if step 4 care or higher is required.
- Consider consultation at step 3.

### Persistent Asthma: Daily Medication

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Preferred: SABA PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Preferred: Low-dose ICS + LABA OR Medium-dose ICS + either LTRA, theophylline, or zileuton</td>
</tr>
<tr>
<td>Step 3</td>
<td>Preferred: Medium-dose ICS + LABA Alternative: Low-dose ICS + either LTRA, theophylline, or zileuton</td>
</tr>
<tr>
<td>Step 4</td>
<td>Preferred: High-dose ICS + LABA AND Consider omalizumab for patients who have allergies</td>
</tr>
<tr>
<td>Step 5</td>
<td>Preferred: High-dose ICS + LABA AND Consider omalizumab for patients who have allergies</td>
</tr>
<tr>
<td>Step 6</td>
<td>Preferred: High-dose ICS + LABA</td>
</tr>
</tbody>
</table>

### Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA > 2 d/wk for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

### Assess control
- Step up if needed (Check adherence, environmental control, comorbid conditions)
- Step down if possible (asthma is well controlled at least 3 mo)

### Notes
- Each step: Patient education, environmental control, management of comorbidities
- Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes)

---

Choosing initial therapy

- Based on the severity of symptoms at presentation/diagnosis
- “Rule of two’s” continues to apply
Initial controller treatment for adults, adolescents and children 6–11 years

- Start controller treatment early
  - For best outcomes, initiate controller treatment as early as possible after making the diagnosis of asthma
- Indications for regular low-dose ICS - any of:
  - Asthma symptoms more than twice a month
  - Waking due to asthma more than once a month
  - Any asthma symptoms plus any risk factors for exacerbations
- Consider starting at a higher step if:
  - Troublesome asthma symptoms on most days
  - Waking from asthma once or more a week, especially if any risk factors for exacerbations
- If initial asthma presentation is with an exacerbation:
  - Give a short course of oral steroids and start regular controller treatment (e.g. high dose ICS or medium dose ICS/LABA, then step down)
Step 2 – low-dose controller + as-needed inhaled SABA

*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
Low, medium and high dose inhaled corticosteroids
Adults and adolescents (≥12 years)

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Total daily dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Beclometasone dipropionate (CFC)</td>
<td>200–500</td>
</tr>
<tr>
<td>Beclometasone dipropionate (HFA)</td>
<td>100–200</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>200–400</td>
</tr>
<tr>
<td>Ciclesonide (HFA)</td>
<td>80–160</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI or HFA)</td>
<td>100–250</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>110–220</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400–1000</td>
</tr>
</tbody>
</table>

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects
LTRA’s in one slide

- Inferior to addition of LABA to ICS in the large majority of trials
- Has been suggested that improved adherence to pills compared to inhalers is an advantage
- No readily available method to predict who will respond
- Try it and see – generic soon!
How often should asthma be reviewed?
- 1-3 months after treatment started, then every 3-12 months
- During pregnancy, every 4-6 weeks
- After an exacerbation, within 1 week

Stepping up asthma treatment
- *Sustained step-up*, for at least 2-3 months if asthma poorly controlled
  - Important: first check for common causes (symptoms not due to asthma, incorrect inhaler technique, poor adherence)
- *Short-term step-up*, for 1-2 weeks, e.g. with viral infection or allergen
  - May be initiated by patient with written asthma action plan
- *Day-to-day adjustment*
  - For patients prescribed low-dose ICS/formoterol maintenance and reliever regimen*

Stepping down asthma treatment
- Consider step-down after good control maintained for 3 months
- Find each patient’s minimum effective dose, that controls both symptoms and exacerbations

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol
Stepping down therapy

- With the exception of those patients with severe asthma or at high risk for severe exacerbations, all asthma patients should be considered for stepping down therapy once well controlled.
- Should not take adult patients completely off ICS, however.
Stepping down therapy

- If a patient exhibits good control for over 3 months, consider stepping down therapy
- Ideally should try to identify the lowest amount of medication necessary to maintain control
- Can also cycle seasonally for those with allergic asthma
Why is my patient’s asthma not controlled?

- Maybe their asthma is that bad
- Other issues are more likely
- Compliance?
  - Can they use their inhalers? (80%)
  - Do they know what they are for?
  - Do they know how important it is?
  - Can they afford them?
Why is my patient’s asthma not controlled?

- Uncontrolled comorbidities?
- Obesity?
- Is it even asthma?
Asthma mimics

- Vocal cord dysfunction (VCD):
  - Will commonly have dysphonia and *inspiratory* wheezing
  - Respond poorly to standard therapy
  - Diagnosed via laryngoscopy
Follow up

- Other essential components of asthma management include:
  - Serial peak flow measurements or symptom diaries (for at-risk patients)
  - Patient education
  - Action plan (written)
When to consider specialist referral

- 2 major reasons:
  - Diagnostic
  - Therapeutic
When to refer – Dx

- Diagnosis is in question
- Atypical symptoms
- Complicating features (GERD, VCD, ABPA, nasal polyps, etc)
- Need for further testing
- Possible occupational asthma
When to refer - therapy

- Life-threatening exacerbation or more than 2 bursts of steroids/yr
- Poor control even with step 4 or higher therapy
- Considering immunotherapy
- Need for education/counseling
Exacerbations

- The first rule of treating an exacerbation (esp. in a high risk patient) is to not underestimate its severity.
 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 $O_2$ 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 $O_2$ saturation (on air) <90% PEF ≤50% predicted or best

 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%)

 LIFE-THREATENING  Drowsy, confused or silent chest

 TRANSFER TO ACUTE CARE FACILITY  While waiting: give SABA, $O_2$, systemic corticosteroid

 WORSENING  URGENT
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%)

TRANSFER TO ACUTE CARE FACILITY

While waiting: give SABA, O₂, systemic corticosteroid

CONTINUE TREATMENT with SABA as needed

ASSESS RESPONSE AT 1 HOUR (or earlier)

IMPROVING

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?
Exacerbations

- Corticosteroid dosing:
- Putting a method to the madness
Exacerbations

- Corticosteroid dosing:
  - Prednisone/prednisolone
    - 1mg/kg to a maximum of 50mg (adults)
    - 1-2 mg/kg, max. 40 mg (children)
    - Treat for 5-7 days, without a taper
  - Medrol dosepaks have no role or even an actual physiologic or pharmacologic basis in lung disease
Exacerbations

- Unlike COPD, antibiotics are not indicated or thought to be beneficial.
- Depending on the current controller medication, it should be increased immediately and continued at the higher dose for at least 2-12 weeks.
- Symbicort (low dose) can be used as a combination controller/rescue inhaler short term.
Optimize dose of ICS/LABA
- Complete resistance to ICS is rare
- Consider therapeutic trial of higher dose

Consider low dose maintenance oral corticosteroids
- Monitor for and manage side-effects, including osteoporosis

Add-on treatments without phenotyping
- Theophylline, LTRA – limited benefit
- Tiotropium – not yet approved for asthma by a major regulator

Phenotype-guided treatment
- Sputum-guided treatment to reduce exacerbations and/or steroid dose
- Severe allergic asthma: suggest add-on anti-IgE treatment (omalizumab)
- Aspirin-exacerbated respiratory disease: consider add-on LTRA

Non-pharmacological interventions
- Consider bronchial thermoplasty for selected patients
- Comprehensive adherence-promoting program

For detailed guidelines, see Chung et al, ERJ 2014
Severe asthma and other therapies

- In most cases patients with severe asthma in whom these therapies are being considered should be referred to a specialist before starting them.
Other therapies

- Omalizumab (Xolair)
- Anticholinergics
- Bronchial thermoplasty
Omalizumab (Xolair)

- A monoclonal antibody against IgE
- Prevents its interaction with basophils and mast cells
- This pathway is not inhibited by steroids
- Does not interact with bound IgE, so of no value in acute asthma
INNOVATE trial, 2005

- 419 patients on at least high-dose ICS + LABA
- 20% were on chronic prednisone
- 26% reduction in exacerbations
- ~50% in hospitalizations
- NNT to prevent one exacerbation: 2.2

Omalizumab

- Typical criteria
- 12 years of age or older
- Inadequate control with ICS + LABA (step 4 or 5)
- Skin or serum allergen testing positive for a year-round allergen such as dust mites, molds, animal dander, *et cetera*
- An elevation in total serum IgE
IgE levels

- Typically 30-700 IU/mL
- Dosing is based on weight and IgE
- Theoretically, levels above 700 are too high and would overwhelm the omalizumab
- In practice many ignore this ceiling and give the highest dose
### Omalizumab Doses (mgs) Administered SQ Injection Every 4 Weeks (≥12 Years of Age)

<table>
<thead>
<tr>
<th>Baseline IgE IU/mL</th>
<th>Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-60</td>
</tr>
<tr>
<td>30-100</td>
<td>150</td>
</tr>
<tr>
<td>&gt;100-200</td>
<td>300</td>
</tr>
<tr>
<td>&gt;200-300</td>
<td>300</td>
</tr>
</tbody>
</table>

Administered Every 2 Weeks

### Omalizumab Doses (mgs) Administered SQ Injection Every 2 Weeks (≥12 Years of Age)

<table>
<thead>
<tr>
<th>Baseline IgE IU/mL</th>
<th>Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-60</td>
</tr>
<tr>
<td>&gt;100-200</td>
<td></td>
</tr>
<tr>
<td>&gt;200-300</td>
<td>225</td>
</tr>
<tr>
<td>&gt;300-400</td>
<td>225</td>
</tr>
<tr>
<td>&gt;400-500</td>
<td>300</td>
</tr>
<tr>
<td>&gt;500-600</td>
<td>300</td>
</tr>
<tr>
<td>&gt;600-700</td>
<td>375</td>
</tr>
</tbody>
</table>
Follow up

- Patients need to be monitored closely for anaphylaxis when the drug is given and should have an epi-pen.
- Patients should be kept on the drug for 12-16 weeks to determine whether or not they will respond.
Bronchial thermoplasty

- Bronchoscopic procedure in which bronchial smooth muscle mass is reduced by (essentially) RF ablation
- Series of 3 procedures
- Not covered by most insurances
- Carries an increased risk of asthma exacerbation immediately after the procedure
Bronchial thermoplasty

- FDA labeling is for “severe persistent asthma inadequately controlled on ICS + LABA”
- It’s current role in therapy is highly controversial
- Many interventionalists use the AIR2 study inclusion criteria
Simplified AIR2 criteria

- High dose ICS + LABA
- Oral steroids OK if stable dose
- MTX and others excluded
- Less than 3 hospitalizations or 4 pulses of oral steroids in last year
- Stable meds for 4+ weeks
- Nonsmokers (<10 pack-years)

Tiotropium (Spiriva)

- FDA approved for COPD
- TALC trial was a noninferiority study with 3 arms (210 patients on low-dose ICS alone at baseline)
  - Double dose of ICS
  - Add LABA to low-dose ICS
  - Add tiotropium to low-dose ICS

TALC trial

- Tiotropium was at least non-inferior to adding a LABA to low-dose ICS in all outcomes
- Tiotropium was superior to doubling the dose of ICS in almost all of the outcomes (so is LABA)
- So: Tiotropium = LABA

Ipratropium (Atrovent)

- Ipratropium has weak data supporting use as an alternative to albuterol for those who cannot tolerate it
- Has been shown to have additive benefit to albuterol in treatment of moderate-severe exacerbations
- Not much to suggest any other role in asthma therapy
Special topics

- Pregnancy
- AERD
Pregnancy and asthma

- 1/3 of pregnant women have worse asthma control, 1/3 better control, 1/3 no change
- Exacerbations, however, are common, especially in the second trimester
Pregnancy and asthma

- The general principle of treating a pregnant patient with asthma is that poorly controlled asthma is a much greater threat to the fetus than any medications.
- Inhaled budesonide (pulmicort) is pregnancy category B and is the preferred ICS.
- All other ICS’ are category C.
Pregnancy and asthma

- LTRA’s (zafirlukast/montelukast) are also category B
- Zileuton should be avoided
- LABA’s are category C based on oral high-dose animal studies (use when benefit outweighs risk)
- Omalizumab is also category B
Pregnancy and asthma

- Oral corticosteroids are indicated for severe exacerbations or if the patient is steroid-dependant at baseline, again on the premise that uncontrolled asthma is the greater risk
- No definite link to adverse maternal or fetal outcomes
Pregnancy and asthma

- Bottom line: Asthma is bad for the baby
- The management table (EPR-3) for pregnant/breastfeeding patients is virtually identical to the normal one
- The key is to monitor the patients very closely and use the lowest doses possible
### Stepwise Approach for Managing Asthma During Pregnancy and Lactation: Treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Severity</th>
<th>Clinical Features Before Treatment or Adequate Control</th>
<th>Medications Required To Maintain Long-Term Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Symptoms/Day PEFR or FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Symptoms/Night PEFR or FEV&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Severe/ Persistent</td>
<td>Continual ≥60%</td>
<td>Frequent &lt;30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily &gt;60%–86%</td>
<td>&gt;1 night/week &gt;30%</td>
</tr>
<tr>
<td>3</td>
<td>Moderate/Persistent</td>
<td>&gt;2 days/week but &lt;daily ≥80%</td>
<td>&gt;2 nights/month 20%–30%</td>
</tr>
<tr>
<td>2</td>
<td>Mild/Persistent</td>
<td>≥2 days/week but &lt;daily ≥80%</td>
<td>&gt;2 nights/month ≥80%</td>
</tr>
<tr>
<td>1</td>
<td>Mild/Intermittent</td>
<td>≥2 days/week but &lt;daily ≥80%</td>
<td>&gt;2 nights/month &lt;20%</td>
</tr>
</tbody>
</table>

#### Daily Medications

- **Preferred treatment:**
  - High-dose inhaled corticosteroids
  - Short-acting inhaled beta<sub>2</sub>-agonist
  - Oral corticosteroids

- **Alternative treatment:**
  - Long-acting inhaled beta<sub>2</sub>-agonist
  - Sustained-release theophylline to serum concentration of 5–12 mcg/mL

#### Quick Relief All Patients

- Short-acting bronchodilator: 2–4 puffs of short-acting inhaled beta<sub>2</sub>-agonist as needed for symptoms.
- Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment may be needed. Course of systemic corticosteroids may be needed.
- Use of short-acting inhaled beta<sub>2</sub>-agonist ≥2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term control therapy.

### Notes

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Classify severity: assigns patient to most severe step in which any feature occurs (PEF is percent of personal best; FEV<sub>1</sub> is percent predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids), then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta<sub>2</sub>-agonist (e.g., use of approximately one canister per month even if not using it every day indicates inadequate control of asthma and the need to initiate or intensify long-term control therapy).
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens, irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if Step 4 care is required. Referral may be considered if Step 3 care is required.

* There are more data on using bronchodilators during pregnancy than on using other inhaled corticosteroids.

† There are minimal data on using leukotriene receptor antagonists in humans during pregnancy; although there are reassuring animal data submitted to FDA.

‡ There are more data on using adenosine than on using other short-acting inhaled beta<sub>2</sub>-agonists.
AERD

- Aspirin Exacerbated Respiratory Disease
- Aka Samter’s triad
- Actually a tetrad: Asthma, nasal polyps, ASA allergy, and persistent rhinosinusitis
AERD

- 10-20% of asthmatics
- 30-40% of asthmatics with nasal polyps
AERD

- Either the asthma or sinusitis can present first
- Gold standard for diagnosis is an ASA challenge
- History of an asthma attack following taking aspirin is suggestive but 16% of patients who give such a history have a negative challenge
AERD: Treatment

- 2 main treatment options
  - Avoidance of all NSAIDS/COX-1 inhibitors
  - ASA desensitization and continuous therapy
  - Leukotriene antagonists?
Leukotriene antagonists

- Thought to be beneficial and possibly very effective as add-on therapy with ASA desensitization
- ASA therapy is most clearly effective for the sinus disease
- LTRA’s work almost exclusively in the lower airways (except zileuton)
ASA desensitization

- First case report from 1922
- Multiple trials have shown improvement in both sinus and respiratory symptoms with asa therapy
- Also a decrease in steroid use and exacerbations
ASA desensitization

- Why does it work?
- ASA allergy is not the underlying mechanism
- It is a marker for an unspecified defect of arachidonic acid metabolism
- High-dose ASA therapy modulates these pathways (IL-4?)
Questions?

- Guidelines available at:
- EPR-3 & pregnancy: nhlbi.nih.gov/guidelines/asthma
- GINA: ginasthma.org