Learning the Asthma Guidelines by Case Studies

Timothy Craig, DO
Professor of Medicine and Pediatrics
Distinguished Educator
Penn State University
Hershey Medical Center
Objectives

1. Learn the Asthma Guidelines
2. Be able to classify asthma severity
3. Be able to determine asthma control
4. Be able to successfully treat asthma
5. Be able to improve patient outcomes
6. Pass your boards
• 19 yo male with asthma since age 5
• Presents with EIB and year round nasal congestion
• Denies daytime symptoms
• Night time symptoms 2 times per month
• Uses albuterol pre-exercise only
• He has moderate limitation on ability to exercise despite albuterol
• No ER visits or Hospitalizations
• **What is his asthma severity?**
• **What would you do now?**
• What is his asthma severity?
  a. Mild intermittent asthma
  b. Mild persistent asthma
  c. Moderate persistent persistent asthma
  d. Severe persistent asthma

Ans:
What is his asthma severity?

- a. Mild intermittent asthma
- b. Mild persistent asthma
- c. Moderate persistent asthma
- d. Severe persistent asthma

Ans: C
### Classification of Asthma Severity
(Youths ≥12 of age and adults)

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-19 yr 85%</td>
<td>&lt;2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>20-39 yr 80%</td>
<td>&lt;2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>40-59 yr 75%</td>
<td>&lt;2 days/week</td>
<td>&gt;2 days/week but &gt;1x/day</td>
</tr>
<tr>
<td>60-80 yr 70%</td>
<td>&lt;2 days/week</td>
<td>&gt;2 days/week but &gt;1x/day</td>
</tr>
<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>&lt;2x/month</td>
<td>3-4x/month</td>
</tr>
<tr>
<td><strong>Short-acting beta₂-agonist use for symptom control</strong></td>
<td>&lt;2 days/week</td>
<td>&gt;2 days/week but &gt;1x/day</td>
</tr>
<tr>
<td><strong>Interference with normal activity</strong></td>
<td>None</td>
<td>Minor limitation</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>Normal FEV₁ between exacerbations</td>
<td>FEV₁ &gt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &gt;80% predicted</td>
<td>FEV₁/FVC normal</td>
</tr>
<tr>
<td></td>
<td>FEV₁/FVC normal</td>
<td>FEV₁/FVC reduced &gt;5%</td>
</tr>
<tr>
<td><strong>Exacerbations requiring oral systemic corticosteroids</strong></td>
<td>0-1/year</td>
<td>&gt;2 in 1 year</td>
</tr>
</tbody>
</table>

Relative annual risk of exacerbations may be related to FEV₁.
• What would you do now?
  a. Start a LABA
  b. Start a low dose ICS
  c. Start a high dose of ICS with LABA
  d. Start a low dose of ICS with a LABA

Ans:
What would you do now?

a. Start a LABA
b. Start a low dose ICS
c. Start a high dose of ICS with a LABA
d. Start a low dose of ICS with a LABA

Ans: D
Stepwise Approach for Managing Asthma in Patients > 12 Years of Age

**STEP 1**
- **PREFERRED**
  - Low-dose ICS
  - SABA PRN

**STEP 2**
- **PREFERRED**
  - Medium-dose ICS + LABA
  - OR Medium-dose ICS
- **ALTERNATIVE**
  - Low-dose ICS + either LTRA, Theophylline or Zileuton

**STEP 3**
- **PREFERRED**
  - Low-dose ICS
- **ALTERNATIVE**
  - Cromolyn, LTRA, Nedocromil, or Theophylline

**STEP 4**
- **PREFERRED**
  - Medium-dose ICS + LABA
- **ALTERNATIVE**
  - Medium-dose ICS + either LTRA, Theophylline or Zileuton

**STEP 5**
- **PREFERRED**
  - High-dose ICS + LABA

**STEP 6**
- **PREFERRED**
  - Medium-dose ICS + LABA + oral corticosteroid

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

**STEP 7**
- **PREFERRED**
  - High-dose ICS + LABA + oral corticosteroid

**STEP 8**
- **PREFERRED**
  - High-dose ICS + LABA + oral corticosteroid + Omalizumab for patients who have allergies

Intermittent Asthma

Persistent Asthma: Daily Medication

Patient Education and Environmental Control at Each Step

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-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
- Caution: Increasing of β-agonist or use >2x/week for symptoms control indicates inadequate control and the need to step up treatment.

• FVC was 90%, FEV-1 was 80% and his ratio was 85%
• CXR was normal
• Skin tests were positive for house dust mites
• Prescribed a low dose of inhaled steroid and a LABA
• Started on nasal steroid
• Albuterol as needed
• Prednisone for severe asthma
• Educated on technique, adherence, acute asthma action plan and mite avoidance
• Returns in 3 month
• He has been using his ICS and LABA regularly
• Denies nighttime, daytime symptoms, or exercise related symptoms
• His QOL is good.
• Albuterol in the last week has been pre-exercise only.
• He used prednisone three times for asthma attacks over the past 12 weeks
• FEV-1 was 80% with a ratio of 83%
• What is his asthma control?
• What would you do?
What is his asthma control?
A. Moderate persistent asthma
B. Well controlled asthma
C. Not well controlled asthma
D. Very poorly controlled

Ans:
• What is his asthma control?
  A. Moderate persistent asthma
  B. Well controlled asthma
  C. Not well controlled asthma
  D. Very poorly controlled

Ans: D
Assessing Asthma Control in Patients ≥12 Years of Age

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classifications of Asthma Control (Youths ≥12 years of age &amp; adults)</th>
<th>Impairment</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
<td>Not Well Controlled</td>
<td>Very Poorly Controlled</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2/month</td>
<td>1-3x/week</td>
<td>≥4x/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Short-acting β₂-agonist use for symptom control</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/personal best</td>
<td>60-80% predicted/personal best</td>
<td>&lt;60% predicted/personal best</td>
</tr>
<tr>
<td>Validated questionnaires*</td>
<td>ATAQ</td>
<td>ACQ</td>
<td>ACT</td>
</tr>
<tr>
<td>3-4</td>
<td>1-2</td>
<td>&gt;1.5</td>
<td></td>
</tr>
<tr>
<td>Risk Exacerbations</td>
<td>0-1/year</td>
<td>&gt;2/per year</td>
<td>&gt;2/per year</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term follow-up care.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What would you do?

a. Add mepolizumab
b. Increase ICS to a high dose and continue the LABA
c. Add a short acting anticholingeric
d. Add zileutin (a lipo-oxygenase inhibitor)
e. Add omalizumab

Ans:
• What would you do?
  a. Add mepolizumab
  b. Increase ICS to a high dose and continue the LABA
  c. Add a short acting anticholingeric
  d. Add zileutin (a lipo-oxygenase inhibitor)
  e. Add omalizumab

Ans: B
Stepwise Approach for Managing Asthma in Patients > 12 Years of Age

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

STEP 1
PREFERRED
Low-dose ICS
SABA PRN

STEP 2
PREFERRED
Low-dose ICS + LABA
ALTERNATIVE
Cromolyn, LTRA, Nedocromil, or Theophylline

STEP 3
PREFERRED
Medium-dose ICS + LABA
ALTERNATIVE
Medium-dose ICS + either LTRA, Theophylline or Zileuton

STEP 4
PREFERRED
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

STEP 5
PREFERRED
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

STEP 6
PREFERRED
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Patient Education and Environmental Control at Each Step

• 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-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.

• Caution: Increasing of β-agonist or use >2x/week for symptoms control indicates
inadequate control and the need to step up treatment.

NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3. Available at:
• Prescribe a peak flow meter
• High dose inhaled corticosteroid plus LABA
• Consider omalizumab or mepolizumab
• SABA PRN and pre-exercise
• Increase albuterol for yellow zone
• Prednisone for red zone
• F/U in 1 month
Primary Endpoint: Rate of Asthma Exacerbations Over 48 Weeks

Protocol-Defined Exacerbation Rate

Placebo | Omalizumab
---|---
0.88 | 0.66

\(\Delta -25\%\)
P = 0.0058*

n = 421
n = 427

*Poisson regression including terms for treatment, concomitant asthma medication strata, dosing regimen, and number of exacerbations in the prior year.
Exacerbations comparing mepolizumab to placebo

Review the Guidelines
# Classifying Severity in Patients ≥12 Years Not Currently Taking Long-Term Controllers

## Components of Severity

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Classification of Asthma Severity (Youths ≥12 of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal FEV₁/FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%</td>
<td></td>
</tr>
<tr>
<td>Impairment</td>
<td>Intermittent</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>• Normal FEV₁ between exacerbations • FEV₁ &gt;80% predicted • FEV₁/FVC normal</td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/year</td>
</tr>
</tbody>
</table>

Relative annual risk of exacerbations may be related to FEV₁
Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

STEP 1
PREFERRED
Low-dose ICS
ALTERNATIVE
SABA PRN

STEP 2
PREFERRED
Low-dose ICS
+ LABA
OR
Medium-dose ICS
ALTERNATIVE
Cromolyn, LTRA, Nedocromil, or Theophylline

STEP 3
PREFERRED
Low-dose ICS + LABA
ALTERNATIVE
Medium-dose ICS + either LTRA, Theophylline or Zileuton

STEP 4
PREFERRED
Medium-dose ICS + LABA
ALTERNATIVE
Medium-dose ICS + either LTRA, Theophylline or Zileuton

STEP 5
PREFERRED
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

STEP 6
PREFERRED
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Patient Education and Environmental Control at Each Step

- 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-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
  - Caution: Increasing of β-agonist or use >2x/week for symptoms control indicates inadequate control and the need to step up treatment.

## Assessing Asthma Control in Patients ≥12 Years of Age

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Control (Youths ≥12 years of age &amp; adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/personal best</td>
</tr>
<tr>
<td>Validated questionnaires*</td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0-1/year</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term follow-up care.</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td></td>
</tr>
</tbody>
</table>
Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age

**STEP 1**
PREFERRED
Low-dose ICS

ALTERNATIVE
Cromolyn, LTRA, Nedocromil, or Theophylline

**STEP 2**
PREFERRED
Low-dose ICS + LABA

ALTERNATIVE
Medium-dose ICS

**STEP 3**
PREFERRED
Low-dose ICS + LABA

ALTERNATIVE
Medium-dose ICS + either LTRA, Theophylline or Zileuton

**STEP 4**
PREFERRED
High-dose ICS + LABA

AND
Consider Omalizumab for patients who have allergies

**STEP 5**
PREFERRED
High-dose ICS + LABA + oral corticosteroid

AND
Consider Omalizumab for patients who have allergies

**STEP 6**
PREFERRED
High-dose ICS + LABA + oral corticosteroid

AND
Consider Omalizumab for patients who have allergies

**Persistent Asthma: Daily Medication**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Interruption of Asthma**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Patient Education and Environmental Control at Each Step**
- 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-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
- Caution: Increasing of β-agonist or use >2x/week for symptoms control indicates inadequate control and the need to step up treatment.

New develops that have been published since the guidelines have been published:

- 1. Tiotropium Bromide can be added in place of a LABA to a moderate to high dose of ICS if the patient is not controlled or to a ICS/LABA combination for poor control.
- 2. Ipratropium bromide can be used in the ED when albuterol use in maximized and patient still has symptoms. This may decrease risk for hospitalization.
- 3. Mepolizumab is approved for severe asthma and inhibits IL-5 and decreases influx of eosinophils into the airway and decrease exacerbations.
- 4. Omalizumab decreases exacerbations and is now approved to use in child.
Increased exacerbations in the beclo group

Decrease response to albuterol in the salmeterol group
Primary Endpoint: Rate of Asthma Exacerbations Over 48 Weeks

![Bar chart showing protocol-defined exacerbation rate for Placebo and Omalizumab](chart.png)

- **Placebo**: 0.88
- **Omalizumab**: 0.66

**Δ –25%**

*P = 0.0058*

n=421 (Placebo)  
n=427 (Omalizumab)

*Poisson regression including terms for treatment, concomitant asthma medication strata, dosing regimen, and number of exacerbations in the prior year.*
Percent reduction in protocol-defined asthma exacerbation rate (mean, 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>FeNO</th>
<th>Eosinophils</th>
<th>Periostin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;19.5 ppb</td>
<td>≥19.5 ppb</td>
<td>&lt;260/µL</td>
</tr>
<tr>
<td>n = 193</td>
<td>-16</td>
<td>-53</td>
<td>-9</td>
</tr>
<tr>
<td>n = 201</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P = 0.45*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.001*</td>
</tr>
</tbody>
</table>

Exacerbation rates

<table>
<thead>
<tr>
<th></th>
<th>Low FeNO at baseline</th>
<th>High FeNO at baseline</th>
<th>Low eosinophils at baseline</th>
<th>High eosinophils at baseline</th>
<th>Low periostin at baseline</th>
<th>High periostin at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.60</td>
<td>0.50</td>
<td>0.65</td>
<td>0.70</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.71</td>
<td>1.07</td>
<td>0.72</td>
<td>1.03</td>
<td>0.72</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Postbronchodilator FEV₁ (%) vs. Month for Mepolizumab and Placebo groups. The graph shows a significant difference in postbronchodilator FEV₁ (%) between the two groups, with Mepolizumab group showing a higher FEV₁ (%) compared to the Placebo group. The p-value is 0.35, indicating no significant difference between the groups.


- 5 year follow-up of patients in AIRE2 Trial (Asthma Intervention Research 2)
- Double-blind, sham-controlled, randomized trial of BT
  - 32% reduction in exacerbations
  - 84% reduction in ED visits
  - 66% reduction in time lost from work
Other new developments that have been published since the guidelines have been published:

- Montelukast is not as effective as ISC, but compliance is better and for this reason over many years the benefits may be equal to ICS (NEJM)
- Montelukast is not as effective as adding LABA to ICS, but due to better compliance over many years the benefits may be equal to adding LABA to ICS (NEJM)
- Aerobic exercise is effective in reducing asthma symptoms
- Vitamin D deficiency is common in asthma and replacement may decrease steroid resistance.
- Adding macrolides may not be of significant benefit in most asthma patients
What is important about the guidelines

• Severity classification followed by control.
• Assess impairment and risk
• Ages 0 to 4, 5 to 12 and greater than 12.
• Addition of functional ability and exacerbations to both severity and control.
• Stresses that ICS are the drug of first choice.
• Addition of omalizumab and zileutin.
Assessing Asthma Control: “Rules of Two”

- If the answer to following questions is yes, a long term controller may be needed or you need to increase care
  - Do you take your quick relief inhaler more than TWO TIMES A WEEK?
  - Do you awaken at night with asthma more than TWO TIMES A MONTH?
  - Do you have daytime symptoms more than twice a week?
  - Do you have attacks more than twice a year
  - OR is there any limitation on exercise or QOL
Summary: what is stressed in the guidelines

- Severity classification on first visit.
- Asthma control on subsequent visits.
- Different guidelines for ages 0 to 4, 5 to 12 and greater than 12.
- Addition of functional ability and exacerbations to both severity and control.
- Stresses that ICS are the drug of first choice.
- Addition of omalizumab or mepolizumab for severe uncontrolled asthma.
- Addition of zileutin for moderate asthma.
- Increase importance of prednisone for severe asthma and very poorly controlled asthma.
Thank you and enjoy your day.

Tim

tcraig@psu.edu