

## Asthma Management

### Case related questions.

#### Scenario:

Mr. Weezer is a 24-year-old man with a history of childhood asthma (one hospitalization as a child, no intubations). He has allergic rhinitis for which he takes loratadine prn, but he had been on no other medications until he presented to the emergency department (ED) with wheezing, dyspnea, and cough approximately 1 month ago. He was treated with albuterol and ipratropium nebulizers and was given intravenous methylprednisolone in the ED. He was subsequently discharged on a prednisone taper and given a Symbicort inhaler to use prn. He now presents for initial outpatient assessment. He completed the prednisone taper 3 weeks ago. Since then, he has reported wheezing requiring Symbicort 3-4 times per week. Once in the past 3 weeks, he awoke in the middle of the night with wheezing and dyspnea; he took Symbicort with improvement in his symptoms. He feels well today.

**Question 1:** Assuming the prior diagnosis of asthma is correct, how would you classify his asthma severity? What objective data do we need to classify his asthma severity?

**Question 2:** How would you classify the asthma severity of the following patients? Assume all have had diagnostic testing to confirm asthma at some point.

- A. Ms. Coughlin has symptoms requiring albuterol once every two weeks or so. She denies nocturnal symptoms. Forced expiratory volume in one second (FEV1) is 95% predicted, with a normal Forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio. She has had two exacerbations in the past eight months requiring steroids.
- B. Mr. Huffington takes a high dose of inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) twice daily but awakens every night with dyspnea, cough, and wheezing. He takes albuterol when these symptoms occur, with symptomatic relief. FEV1 is 75% predicted with a decreased FEV1/FVC ratio. He has not received systemic steroids in the past year.
- C. Ms. Short-Brett presents with symptoms most days in a week and nocturnal awakening twice per week. She has stopped taking the subway to work since it is too difficult to climb the stairs. FEV1 is 90% predicted with a normal FEV1/FVC ratio. She has had one exacerbation requiring prednisone in the past year. She is started on twice daily and prn low dose ICS-formoterol. When she returns to see you, she has symptoms 1-2 days per week, but no nocturnal symptoms.

**Question 3:** What treatment do the guidelines recommend for each of the above patients?

**Question 4:** Mr. Weezer's insurance did not cover single maintenance and reliever therapy (SMART) (did not cover ICS-formoterol), and he was started on a different low-dose ICS-LABA (step 3) and now returns for a follow-up one month later. He still reports needing albuterol 3 times per week, with 1 or 2 awakenings over the past month because of asthma symptoms. FEV1 is 75% predicted. What is your next step?

**Question 5:** Mr. Weezer had misunderstood the initial instructions and had just been using the ICS-LABA prn along with albuterol. You do more teaching during his follow-up visit, and when he returns after another month, he reports almost complete resolution of his symptoms since taking the ICS-LABA as prescribed. He has only needed albuterol twice in the entire month. His FEV1 is now 105% predicted. What is your next step?

**Question 6:** What triggers should you evaluate and consider treating for?

**Question 7:** For whom would you consider biologic therapy, and what diagnostic testing do you need to initiate this? How long should you continue therapy before deciding it isn't working? What monitoring should you do for a patient on biologics?

## Asthma Management

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### Educational Objectives:

1. Review clinical guidelines for asthma assessment, including subtleties that may be tested on boards
2. Review guidelines for step-wise asthma therapy,<sup>1</sup> and identify similarities and differences between the National Heart, Lung and Blood Institute's (NHLBI) National Asthma Education and Prevention Program Coordinating Committee (NAEPCC) Expert Panel 4 (EPR-4) Working Group classification<sup>2</sup> and Global Initiative for Asthma (GINA) guidelines<sup>3</sup>
3. Discuss indications for the initiation of biologic therapy

### Scenario:

Mr. Weezer is a 24-year-old man with a history of childhood asthma (one hospitalization as a child, no intubations). He has allergic rhinitis for which he takes loratadine prn, but he had been on no other medications until he presented to the ED with wheezing, dyspnea, and cough approximately 1 month ago. He was treated with albuterol and ipratropium nebulizers and was given intravenous methylprednisolone in the ED. He was subsequently discharged on a prednisone taper and given a Symbicort inhaler to use prn. He now presents for initial outpatient assessment. He completed the prednisone taper 3 weeks ago. Since then, he has reported wheezing requiring Symbicort 3-4 times per week. Once in the past 3 weeks, he awoke in the middle of the night with wheezing and dyspnea; he took Symbicort with improvement in his symptoms. He feels well today.

**Question 1: Assuming the prior diagnosis of asthma is correct, how would you classify his asthma severity? What objective data do we need to classify his asthma severity?**

Prior to answering this, we should think about the differences and similarities between the NHLBI NAEPPCC EPR-4 guidelines<sup>2</sup> and the GINA recommendations.<sup>3</sup>

The NHLBI NAEPPCC EPR-4 update was published in 2020 and reviews six key topics based on data prior to 2016.<sup>2</sup> The international GINA recommendations are comprehensive and updated yearly based on the prior year's scientific data.<sup>3</sup> The NHLBI guidelines and GINA recommendations have some similarities but do differ particularly related to the approach to classifying asthma severity, treatment of mild asthma, and slightly different approaches to step therapy. Treatment is guided by severity classification in the NHLBI guidelines whereas symptoms guide therapy choices according to the GINA recommendations. GINA suggests severity should be assessed retrospectively from the level of treatment required to control the patient's exacerbations and symptoms.<sup>2</sup>

**Severe asthma:** Asthma that remains uncontrolled despite a high dose of inhaled corticosteroid-long acting beta agonist (ICS-LABA) or requires a high dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma should be distinguished from difficult-to-treat asthma due to inadequate treatment, comorbid conditions, or poor adherence to therapy.

**Moderate asthma:** Asthma that is well controlled with low or medium dose ICS-LABA.

**Mild asthma:** Asthma that is well controlled with as-needed ICS-formoterol or with low-dose ICS plus as-needed short-acting beta agonist (SABA).

In contrast, NHLBI considers severity to be the intrinsic intensity of disease, with severity determined by components of impairment and future risk, often assessed immediately after diagnosis and ideally prior to the initiation of controller medications (Figure 1).<sup>1</sup>

**Figure 1.** Classifying Asthma Severity and Initiating Treatment

# Classifying Asthma Severity & Initiating Treatment in Youths ≥12 Years of Age & Adults

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

| Components of Severity                  |                                                                                         | Classification of Asthma Severity: Youths ≥12 Years of Age & Adults                                                                                                                                                  |                                                                                                                          |                                                                                                                                             |                                                                                                                                 |
|-----------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
|                                         |                                                                                         | Intermittent                                                                                                                                                                                                         | Persistent                                                                                                               |                                                                                                                                             |                                                                                                                                 |
|                                         |                                                                                         |                                                                                                                                                                                                                      | Mild                                                                                                                     | Moderate                                                                                                                                    | Severe                                                                                                                          |
| Impairment                              | Symptoms                                                                                | ≤2 days/week                                                                                                                                                                                                         | >2 days/week but not daily                                                                                               | Daily                                                                                                                                       | Throughout day                                                                                                                  |
|                                         | Nighttime awakenings                                                                    | ≤2x/month                                                                                                                                                                                                            | 3–4x/month                                                                                                               | >1x/week but not nightly                                                                                                                    | Often 7x/week                                                                                                                   |
|                                         | Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB) | ≤2 days/week                                                                                                                                                                                                         | >2 days/week but not daily, and not more than 1x on any day                                                              | Daily                                                                                                                                       | Several times per day                                                                                                           |
|                                         | Interference with normal activity                                                       | None                                                                                                                                                                                                                 | Minor limitation                                                                                                         | Some limitation                                                                                                                             | Extremely limited                                                                                                               |
|                                         | Lung function                                                                           | <ul style="list-style-type: none"> <li>• Norm. FEV<sub>1</sub> between exacerbations</li> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC normal</li> </ul>                                   | <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> ≥80% predicted</li> <li>• FEV<sub>1</sub>/FVC normal</li> </ul> | <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;60% but &lt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC reduced 5%</li> </ul> | <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% predicted</li> <li>• FEV<sub>1</sub>/FVC reduced 5%</li> </ul> |
| Risk                                    | Exacerbations requiring oral systemic corticosteroids                                   | 0–1/year (see note)                                                                                                                                                                                                  | ≥2 in 1 year (see note)                                                                                                  |                                                                                                                                             |                                                                                                                                 |
|                                         |                                                                                         | Consider severity & interval since last exacerbation. Frequency & severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV <sub>1</sub> . |                                                                                                                          |                                                                                                                                             |                                                                                                                                 |
| Recommended Step for Initiating Therapy |                                                                                         | Step 1                                                                                                                                                                                                               | Step 2                                                                                                                   | Step 3                                                                                                                                      | Step 4 or Step 5                                                                                                                |
|                                         |                                                                                         | In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.                                                                                                                      |                                                                                                                          |                                                                                                                                             |                                                                                                                                 |

**Notes:**

- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had >2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

NHLBI's Guidelines for the Diagnosis and Treatment of Asthma. The National Asthma Education and Prevention Program Expert Panel Report 3. NIH 2007.<sup>1</sup>

According to NHLBI guidelines, Mr. Weezer would be considered to have mild persistent asthma and this classification will guide therapy choices.

**Question 2: How would you classify the asthma severity of the following patients? Assume all have had diagnostic testing to confirm asthma at some point.**

- A. Ms. Coughlin has symptoms requiring albuterol once every two weeks or so. She denies nocturnal symptoms. FEV1 is 95% predicted, with a normal FEV1/FVC ratio. She has had two exacerbations in the past eight months requiring steroids.**

While reported symptoms suggest mild intermittent asthma, our patient required two courses of steroids in the past year and is therefore classified as mild persistent asthma (per NHLBI).

- B. Mr. Huffington takes a high dose of ICS/LABA twice daily but awakens every night with dyspnea, cough, and wheezing. He takes albuterol when these symptoms occur, with symptomatic relief. FEV1 is 75% predicted with a decreased FEV1/FVC ratio. He has not received systemic steroids in the past year.**

He would be considered to have severe persistent asthma per NHLBI given frequency of symptoms.

Assuming he is using his medications correctly and has no comorbidities that are contributing to his symptoms, he would also be considered to have severe asthma by GINA as he remains uncontrolled despite a high dose ICS/LABA twice daily.

- C. Ms. Short-Brett presents with symptoms most days in a week and nocturnal awakening twice per week. She has stopped taking the subway to work since it is too difficult to climb the stairs. FEV1 is 90% predicted with a normal FEV1/FVC ratio. She has had one exacerbation requiring prednisone in the past year. She is started on twice daily and prn low dose ICS-formoterol. When she returns to see you, she has symptoms 1-2 days per week, but no nocturnal symptoms.**

Per NHLBI guidelines, at initial presentation she has moderate persistent asthma that becomes well controlled after starting low dose ICS-formoterol.

Per GINA recommendations, she has moderate asthma because she is controlled with a low dose of ICS-LABA.

**Question 3: What treatment do the guidelines recommend for each of the above patients?**

As mentioned before, treatment is guided by severity classification in the NHLBI guidelines whereas symptoms guide therapy choices according to the GINA recommendations. See Figure 2 below to compare the different recommendations for NHLBI NAEPPCC step therapy and GINA step therapy. See the end of this document for the separate tables (Figure 4 and Figure 5).

**Figure 2.** Comparison of NAEPP and GINA Guidelines for Step Therapy in Asthma.<sup>4</sup>

|        | NAEPP                                                       |                                                                                    | GINA 2022                                                                                 |                                                                                                                                               |
|--------|-------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
|        | Severity classification guides therapy choices <sup>a</sup> | Preferred therapy <sup>b</sup>                                                     | Symptoms guide therapy choices                                                            | Preferred therapy <sup>c</sup>                                                                                                                |
| Step 1 | Intermittent                                                | SABA as needed                                                                     | Symptoms < 2 times/ mo; no risk factors for exacerbations; no exacerbations in past 12 mo | As-needed low-dose ICS-formoterol                                                                                                             |
| Step 2 | Mild persistent                                             | Daily low-dose ICS, and SABA as needed<br>OR<br>Concomitant ICS and SABA as needed |                                                                                           |                                                                                                                                               |
| Step 3 | Moderate persistent                                         | Daily and as-needed low-dose ICS-formoterol (SMART)                                | Symptoms occur most days (eg, 4-5 d/wk); or waking at night ≥ 1x/wk                       | Daily and as-needed low-dose ICS-formoterol (SMART)                                                                                           |
| Step 4 | Severe persistent                                           | Daily and as-needed medium-dose ICS-formoterol (SMART)                             | Severely uncontrolled asthma presentation, or acute exacerbation                          | Daily and as-needed low-dose ICS-formoterol (SMART)                                                                                           |
| Step 5 |                                                             | Daily medium- to high-dose ICS-LABA + LAMA; and SABA as needed                     |                                                                                           | Daily and as-needed medium-dose ICS-formoterol (SMART) + LAMA; refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLPR |
| Step 6 |                                                             | Daily high-dose ICS-LABA + oral systemic corticosteroids; and SABA as needed       | N/A                                                                                       | N/A                                                                                                                                           |

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL4R, interleukin 4 receptor; IL5/5R, interleukin 5 or its receptor; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting beta-2 agonist; SMART, single maintenance and reliever therapy; TSLPR, thymic stromal lymphopoietin receptor.

<sup>a</sup> NAEPP Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (2007).

<sup>b</sup> NAEPP 2020 Focused Updates to the Asthma Management Guidelines.

<sup>c</sup> GINA Global strategy for asthma management and prevention (2022).

### Some important things to note:

- GINA suggests the distinction between mild intermittent and mild persistent asthma is arbitrary, recognizes that adherence to daily ICS use is poor in patients with infrequent symptoms and exposes them to risks of SABA-only treatment, and therefore recommends prn ICS-formoterol which has been shown to reduce exacerbations compared with both SABA only treatment and severe exacerbations compared with daily ICS and prn SABA. GINA does not recommend the use of prn albuterol and instead recommends prn low dose ICS-formoterol for Step 1 and 2 therapy.<sup>3</sup>
- The updated NHLBI document did not address this and continues to recommend prn albuterol for Step 1 therapy and daily low dose ICS and prn SABA for Step 2 therapy.<sup>2</sup>
- Both GINA and the 2020 NHLBI update recommend using a combination inhaled ICS-formoterol inhaler for both maintenance and quick symptoms relief (**SMART** - single maintenance and reliever therapy) for steps 3 and 4 treatments. SMART reduces the risk for severe exacerbations compared with maintenance ICS or ICS-LABA regimens with SABA reliever.<sup>2,3</sup>



- Note that ICS-formoterol is the only studied preparation in clinical trials using SMART therapy. In the United States, this is budesonide-formoterol. An alternative is mometasone-formoterol. The onset of action of formoterol is as rapid as albuterol and has a longer duration of action.
- Note the practical barriers to SMART use in the US: (1) not yet FDA approved, (2) may not be covered by patient's insurance, and (3) insurers may cover only a 30-day supply of maintenance medication at a time.
- GINA recommends use of budesonide-formoterol 160/4.5 ug. "Low dose" is considered one puff, and "medium dose" is two puffs. The recommended total maximum dose that can be taken on any single day (total of maintenance plus prn doses) for budesonide-formoterol 160/4.5 µg is 12 inhalations for age 12 and older, which corresponds to a 54 µg delivered dose of formoterol.<sup>3</sup>

### **Back to our patients-**

#### **Ms. Coughlin**

- NHLBI - mild persistent asthma, daily low dose ICS and SABA as needed
- GINA - as needed ICS-formoterol

#### **Mr. Huffington**

- NHLBI - severe persistent asthma, poorly controlled despite high dose ICS/LABA, add long-acting muscarinic antagonist (LAMA)
- GINA - severe asthma, add LAMA and refer for phenotypic assessment and possible biologics

#### **Ms. Short-Brett**

- NHLBI - moderate persistent asthma, daily and prn low dose ICS-formoterol
- GINA - Per GINA, upon presentation based on her symptoms, the recommendation would also be to start daily and prn low dose ICS-formoterol

Figure 3 below illustrates dosing equivalence for available ICS formulations.

**Figure 3.** Inhaled Steroid Dosing NHLBI’s Guidelines for the Diagnosis and Treatment of Asthma.

| Medication                                                          | Low Daily Dose         |                         |                           | Medium Daily Dose      |                         |                           | High Daily Dose        |                         |                           |
|---------------------------------------------------------------------|------------------------|-------------------------|---------------------------|------------------------|-------------------------|---------------------------|------------------------|-------------------------|---------------------------|
|                                                                     | Child 0–4 Years of Age | Child 5–11 Years of Age | ≥12 Years of Age & Adults | Child 0–4 Years of Age | Child 5–11 Years of Age | ≥12 Years of Age & Adults | Child 0–4 Years of Age | Child 5–11 Years of Age | ≥12 Years of Age & Adults |
| <b>Beclomethasone HFA</b><br>40 or 80 mcg/puff                      | NA                     | 80–160 mcg              | 80–240 mcg                | NA                     | >160–320 mcg            | >240–480 mcg              | NA                     | >320 mcg                | >480 mcg                  |
| <b>Budesonide DPI</b><br>90, 180, or 200 mcg/inhalation             | NA                     | 180–400 mcg             | 180–600 mcg               | NA                     | >400–800 mcg            | >600–1,200 mcg            | NA                     | >800 mcg                | 1,200 mcg                 |
| <b>Budesonide Inhaled</b><br>Inhalation suspension for nebulization | 0.25–0.5 mg            | 0.5 mg                  | NA                        | >0.5–1.0 mg            | 1.0 mg                  | NA                        | >1.0 mcg               | 2.0 mg                  | NA                        |
| <b>Flunisolide</b><br>250 mcg/puff                                  | NA                     | 500–750 mcg             | 500–1,000 mcg             | NA                     | 1,000–1,250 mcg         | >1,000–2,000 mcg          | NA                     | >1,250 mcg              | >2,000 mcg                |
| <b>Flunisolide HFA</b><br>80 mcg/puff                               | NA                     | 160 mcg                 | 320 mcg                   | NA                     | 320 mcg                 | >320–640 mcg              | NA                     | >640 mcg                | >640 mcg                  |
| <b>Fluticasone HFA/MDI</b><br>44, 110, or 220mcg/puff               | 176 mcg                | 88–176 mcg              | 88–264 mcg                | >176–352 mcg           | >176–352 mcg            | >264–440 mcg              | >352 mcg               | >352 mcg                | >440 mcg                  |
| <b>Fluticasone DPI</b><br>50, 100, or 250 mcg/inhalation            | NA                     | 100–200 mcg             | 100–300 mcg               | NA                     | >200–400 mcg            | >300–500 mcg              | NA                     | >400 mcg                | >500 mcg                  |
| <b>Mometasone DPI</b><br>200 mcg/inhalation                         | NA                     | NA                      | 200 mcg                   | NA                     | NA                      | 400 mcg                   | NA                     | NA                      | >400 mcg                  |
| <b>Triamcinolone acetonide</b><br>75 mcg/puff                       | NA                     | 300–600 mcg             | 300–750 mcg               | NA                     | >600–900 mcg            | >750–1,500 mcg            | NA                     | >900 mcg                | >1,500 mcg                |

The National Asthma Education and Prevention Program Expert Panel Report 3. NIH 2007.<sup>1</sup>

**Question 4: Mr. Weezer’s insurance did not cover SMART (did not cover ICS-formoterol), and he was started on a different low-dose ICS-LABA (step 3) and now returns for a follow-up one month later. He still reports needing albuterol 3 times per week, with 1 or 2 awakenings over the past month because of asthma symptoms. FEV1 is 75% predicted. What is your next step?**

Mr. Weezer’s asthma is not controlled. The first thing to do is assess his use of his inhaler. You should review inhaler teaching at each visit, make sure he has a spacer if he is using a metered dose inhaler (MDI), knows to rinse his mouth afterward, and did not stop the ICS-LABA because he was getting thrush or having another problem, etc. If you are convinced that he is using the ICS-LABA as prescribed, then he would be classified as not well controlled, and you should step up therapy by changing to a medium-dose ICS-LABA (i.e., go from step 3 to step 4 in both NHLBI and GINA recs) and reevaluate in the next 2–6 weeks. (Additionally, you should assess environmental factors and manage comorbidities at each visit.)

**Question 5: Mr. Weezer had misunderstood the initial instructions and had just been using the ICS-LABA prn along with albuterol. You do more teaching during his follow-up visit, and when he returns after another month, he reports almost complete resolution of his symptoms since taking the ICS-LABA as prescribed. He has only needed albuterol twice in the entire month. His FEV1 is now 105% predicted. What is your next step?**

He would now be classified as well controlled. Continue current therapy for now, as he has only been on it for one month. If he maintains good symptom control for 3 months, it would be appropriate to discuss stepping-down therapy to a low-dose ICS-LABA (step 2).



## Question 6: What triggers should you evaluate and consider treating for?

In addition to pharmacologic therapy, a key aspect of asthma management is the identification of environmental factors and comorbid conditions that may affect asthma control. Key triggers, including inhaled allergens, irritants, comorbid conditions, and medications, are included in Table 1.

**Table 1.** Environmental Factors and Comorbid Conditions that Affect Asthma Control<sup>1</sup>

| Inhaled Allergens - perennial                                                                                                                                                                                                                                   | Irritants                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Pets</li><li>• Mold</li><li>• Dust mites</li><li>• Cockroaches</li></ul>                                                                                                                                                | <ul style="list-style-type: none"><li>• Tobacco smoke</li><li>• Wood-burning stove/fireplace</li><li>• Perfumes</li><li>• Cleaning agents</li><li>• Workplace exposures</li></ul> |
| Inhaled Allergens - seasonal                                                                                                                                                                                                                                    | Comorbid Conditions                                                                                                                                                               |
| <ul style="list-style-type: none"><li>• Trees (early spring)</li><li>• Grasses (late spring)</li><li>• Weeds (late summer/autumn)</li><li>• Alternaria, Cladosporium, mites (summer/fall)</li><li>• Animal dander (Cold months in temperate climates)</li></ul> | <ul style="list-style-type: none"><li>• Sinusitis/rhinitis</li><li>• Gastroesophageal Reflux (GERD)</li></ul>                                                                     |
|                                                                                                                                                                                                                                                                 | Medications                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"><li>• Non-steroidal Anti-inflammatory Drugs (NSAIDs)</li><li>• Aspirin</li><li>• Beta-blockers</li></ul>                                        |

Because the single biggest risk factor for asthma is sensitization to one of the major indoor allergens, it is appropriate to have a low threshold to evaluate with serum allergen-specific IgE testing and/or refer to an allergist for skin testing. For patients with allergic sensitization and allergic symptoms with mild to moderate allergic asthma, subcutaneous immunotherapy is recommended as an adjunct to standard medications.<sup>2</sup>

## Question 7: For whom would you consider biologic therapy, and what diagnostic testing do you need to initiate this? How long should you continue therapy before deciding it isn't working? What monitoring should you do for a patient on biologics?

If you have optimized management (asthma education, correct inhaler use and adherence, treated comorbidities and modifiable risk factors, and stepped-up therapy) and asthma remains poorly controlled with ongoing exacerbations, consider the initiation of biologic therapy. Diagnostic testing for type 2 inflammatory biomarkers should be performed (elevated absolute eosinophil count, IgE, and fractional exhaled nitric oxide (FeNO)). If the patient has an elevated eosinophil count, it would be appropriate to rule out other causes of eosinophilia (such as allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatous with polyangiitis (EGPA), and parasitic infections). Typical duration of a trial of biologic therapy lasts 4-6 months; monitoring for response is predominantly a clinical assessment. A summary of currently available biologics is listed in Table 2.

**Table 2.** Biologic Agents for the Treatment of Severe Asthma.<sup>3</sup>

| Class      | Medication (route) | Mechanism of action                                                                        | Criteria for approval                                                                    |
|------------|--------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Anti-IgE   | Omalizumab (SC)    | Binds Fc part of free IgE. Reduces IgE levels and down-regulates receptor expression       | IgE level between 30-700 IU/mL and positive allergen testing [RAST or skin testing]      |
| Anti-IL-5  | Mepolizumab (SC)   | Binds circulating IL-5; induces apoptosis of eosinophils                                   | Absolute eosinophil count > 150 cells/microliter                                         |
| Anti-IL-5  | Reslizumab (IV)    | IL-5 antagonist; reduces the production and survival of eosinophils                        | Absolute eosinophil count > 400 cells/microliter                                         |
| Anti-IL-5R | Benralizumab (SC)  | Binds IL-5R alpha subunit and induces apoptosis of eosinophils                             | Absolute eosinophil count > 150 cells/microliter                                         |
| Anti-IL-4R | Dupilumab (SC)     | Binds IL-4Ra; blocks IL-4 and IL-13 signaling                                              | Absolute eosinophil count > 150 cells/microliter                                         |
| Anti-TSLP  | Tezepelumab (SC)   | Binds to TSLP (an epithelial cytokine) and reduces eosinophils, IgE, FeNO, IL-5, and IL-13 | No minimum eosinophils or FeNO required (but greater benefit for higher eos and/or FeNO) |

*TSLP = thymic stromal lymphopoietin; RAST = radioallergosorbent test*

### Special considerations<sup>3</sup>:

- Use of omalizumab for IgE levels greater than 700 IU/mL is considered off-label.
- Omalizumab is associated with a 0.2% chance of anaphylaxis though the odds of a reaction are higher in a person with a prior history of anaphylaxis. For all patients, a prescription for an Epi-Pen is required.
- The most common side effects are injection site reactions (particularly for the subcutaneous routes of administration).
- An initial trial of 4-6 months is suggested for biologic therapy initiation.
- Several biologics have been approved for other indications - omalizumab (chronic spontaneous urticaria, chronic rhinosinusitis with nasal polyposis (CRwNP)), mepolizumab (EGPA, CRwNP, hypereosinophilic syndrome), benralizumab (EGPA), and dupilumab (atopic dermatitis, CRwNP, refractory COPD).
- Tezepelumab can be used in non-Type 2 asthma.



**Figure 5.** NHLBI's 2020 Focused Updates to the Asthma Management Guidelines.

**Figure 1.d:** Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

| Intermittent Asthma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |          | Management of Persistent Asthma in Individuals Ages 12+ Years                                                                                                                                                                                                 |                                                                                                                                                                                                                        |                                                                                                                                                                                                                |                                                                                         |                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | STEP 1   | STEP 2                                                                                                                                                                                                                                                        | STEP 3                                                                                                                                                                                                                 | STEP 4                                                                                                                                                                                                         | STEP 5                                                                                  | STEP 6 <sup>■</sup>                                                 |
| Preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | PRN SABA | Daily low-dose ICS and PRN SABA<br>or<br>PRN concomitant ICS and SABA▲                                                                                                                                                                                        | Daily and PRN combination low-dose ICS-formoterol▲                                                                                                                                                                     | Daily and PRN combination medium-dose ICS-formoterol▲                                                                                                                                                          | Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲                                    | Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA |
| Alternative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |          | Daily LTRA* and PRN SABA<br>or<br>Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA                                                                                                                                                     | Daily medium-dose ICS and PRN SABA<br>or<br>Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA<br>or<br>Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA | Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲<br>or<br>Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA | Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA            |                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |          | Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲ |                                                                                                                                                                                                                        |                                                                                                                                                                                                                | Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)** |                                                                     |
| Assess Control                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |          |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                        |                                                                                                                                                                                                                |                                                                                         |                                                                     |
| <div><div>◀</div><div><ul style="list-style-type: none"><li>First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.</li><li><b>Step up</b> if needed; reassess in 2–6 weeks</li><li><b>Step down</b> if possible (if asthma is well controlled for at least 3 consecutive months)</li></ul><p>Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.</p><p>Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.</p></div><div>▶</div></div> |          |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                        |                                                                                                                                                                                                                |                                                                                         |                                                                     |

**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub>-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta<sub>2</sub>-agonist

<sup>▲</sup> Updated based on the 2020 guidelines.

\* Cromolyn, Nedocromil, LTRAs including Zileuton and montelukast, and Theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

\*\* The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (e.g. anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6.

■ Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

The National Asthma Education and Prevention Program Expert Panel Report 4. NIH 2022

## References:

1. National Asthma Education and Prevention Program. *NHLBI's Guidelines for the Diagnosis and Treatment of Asthma: Expert Panel Report 3*. National Institutes of Health; 2007.
2. National Asthma Education and Prevention Program. *NHLBI's 2020 Focused Updates to the Asthma Management Guidelines: Expert Panel Report 4*. National Institutes of Health; 2022.
3. Global Initiative for Asthma. *Global Strategy for Asthma Prevention and Management*. 2024. Available at: <https://www.ginasthma.org>.
4. Nissly T, Moon J, Ricco J. Comparison of NAEPP and GINA Guidelines for Step Therapy in Asthma. *J Fam Pract*. 2022 Nov;71(9):392-397. doi: 10.12788/jfp.0501. PMID: 36538773.

## Asthma Management

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### Post-Test Case Related Questions

1. A 35-year-old male with a history of asthma presents to your office for a new patient visit. He notes that he has asthma symptoms 3-4 days a week. He denies any nighttime awakenings. He is currently maintained on fluticasone propionate-salmeterol MDI 110/21, one inhalation mcg twice daily, and uses his albuterol once a day for rescue. You reviewed his inhaler technique and adherence, and both are appropriate. His PFTs show an FEV1 of 75% predicted. He has not had any exacerbations in the last year. Which of the following best characterized this patient's asthma severity?
  - a. Severe persistent
  - b. Moderate persistent
  - c. Mild persistent
  - d. More information is needed
2. Given the above patient's symptoms, you escalate the dose of fluticasone so that he is taking a medium dose ICS-LABA. However, he remains poorly controlled with frequent symptoms, and you are considering stepping up therapy again. Which of the following would be the preferred recommended next step in management for his asthma?
  - a. Add an additional ICS inhaler
  - b. Addition of leukotriene receptor antagonist
  - c. Add LAMA to his current ICS-LABA
  - d. Daily use of theophylline
3. A 29-year-old female with a history of allergic rhinitis, eczema, and asthma presents to your clinic for ongoing asthma management. Her symptoms remain poorly controlled, with symptoms throughout the day and almost every night despite high-dose of fluticasone-salmeterol and nightly montelukast. She has required frequent treatments with systemic steroids for asthma exacerbations, and thus, you are considering her candidacy for omalizumab. Her serum IgE level is 900 IU/mL. Which of the following statements is false regarding her eligibility for this medication?
  - a. She can also receive on-label immunotherapy if found to have sensitization to aero-allergens. Her IgE level >700 is a contraindication to administration, though it is occasionally given off-label.
  - b. Allergic sensitization, with positive skin testing or in vitro testing for allergen-specific IgE is necessary.
  - c. A prescription for an EpiPen is required.
  - d. If she has no improvement in symptoms by 4 months, she should be evaluated for another biologic treatment.



## Asthma Management

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### Post-Test Case Related Questions with Answer Key

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