DIAGNOSIS AND MANAGEMENT OF ASTHMA IN ADULTS

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Week 18

Educational Objectives:

1. Apply the clinical criteria for diagnosing and staging asthma
2. Describe the step-wise approach to pharmacologic management of asthma, including indications for use of biologic agents
3. Develop outpatient monitoring plans for patients with asthma

CASE ONE:

Mr. Sean O'Brien is a 29-year-old gentleman who presents to your clinic to establish care after being seen in the emergency department for cough and shortness of breath. He reports being diagnosed with asthma in childhood but has not needed any medications since his early teens and has had no prior ED visits or hospitalization. He moved to Atlanta, Georgia two years ago and subsequently developed new seasonal allergies with frequent sinus congestion and post-nasal drip. Since then, he has noticed intermittent episodes of dry cough and chest pressure, particularly at night. He was seen in the emergency department a week ago because the cough and chest pressure awoke him from sleep, and he felt extremely short of breath with audible wheezing. He was given an albuterol treatment with symptomatic relief and discharged from the ED with an albuterol inhaler. He has needed to use the albuterol inhaler four times at night this past week since returning from the emergency department.

He has a past medical history of eczema. He is not on any medications aside from albuterol. He is a graduate student living on campus with no known environmental exposures at school or at home. He has smoked a quarter pack of cigarettes daily for the last five years. He has no pets.

On exam, his vitals are normal. He is speaking in full sentences and appears comfortable. HEENT exam is notable for bilateral boggy nasal turbinates with scant discharge and cobble-stoning. Pulmonary exam is clear to auscultation without wheezes, rales, or rhonchi. He has no rashes. The remainder of his exam is unremarkable.

Questions:

1. **What is the pathophysiology of asthma?**
   Asthma is a clinically heterogeneous syndrome that typically develops in childhood or adolescence, and is marked by episodes of dyspnea, wheezing, chest tightness, and/or cough.

Several variations of asthma exist, including atopic (allergic) asthma, aspirin-exacerbated asthma, exercise-induced asthma, etc. However, in most cases, an interplay of three pathophysiological mechanisms lead to asthma symptoms -- **variable airway obstruction, airway hyperresponsiveness, and airway inflammation**.

Patients with asthma have fluctuations in airway diameter that cause **variable airway obstruction** over spans of minutes to days as a result of airway secretions, bronchoconstriction, and mucosal inflammation. Airway obstruction should be reversible, although in severe disease, obstruction may be incompletely reversible with bronchodilators.

Nearly all patients also have **hyperresponsive airways** – over-exuberant constriction and inflammation of airways due to stimulation of parasympathetic activity and muscarinic receptors promoting bronchoconstriction. Airway hyperresponsiveness can be triggered by exposure to allergens, chemicals/pollutants, and infections.

Airway inflammation in asthma leads to mucosal edema, increased secretions that can worsen airway hyperresponsiveness and obstruction. Airway inflammation is mediated by a wide array of immune cells. In patients with atopic (allergy-related) asthma, IgE, mast cells, eosinophils, and histamine release play crucial roles in airway inflammation. Patients with non-atopic asthma may have alterations in cytokine pathways leading to reduced endogenous anti-inflammatory factors (McCracken, 2017).

2. **What additional tests should be ordered, if any, to diagnose this patient's symptoms?**
Adults with suspected asthma symptoms should have spirometry ($42, healthcare bluebook) performed in order to receive a formal diagnosis of asthma. Spirometry is an underutilized test in patients diagnosed with asthma. The ACP Choosing Wisely Campaign (http://www.choosingwisely.org/patient-resources/spirometry-for-asthma/), in conjunction with the American Academy of Allergy and Immunology, recommends, "Don't diagnose or manage asthma without spirometry." Relying on symptoms alone can lead one to over- and under-estimate the severity of asthma. Spirometry is particularly helpful in patients with late-onset asthma, as well as in patients with concurrent tobacco use to prevent misdiagnosis of other underlying health conditions. A recent study found that up to one third of patients with a "history of asthma" did not actually have asthma after formal spirometry assessment (Aaron, 2017).

Spirometry should be assessed pre- and post-bronchodilator therapy in a stable patient (do not perform during an exacerbation) to evaluate for reversible airway obstruction. Bronchodilators should not be used within four hours of the initial spirometry attempt. Post-bronchodilator evaluation should be performed 10-15 minutes after delivery of four puffs of albuterol by metered-dose inhaler (MDI) with use of a spacer.

Patients who do not meet the initial criteria for presence of obstructive disease despite a high pretest probability should either undergo methacholine provocation (sensitivity 96.5%, specificity 78.4%) or have repeat spirometry performed on a different day (Yurdakul, 2005). Patients with asthma, particularly those with symptoms of atopy (e.g., seasonal allergies or eczema), should have a CBC with differential collected to evaluate for evidence of

eosinophilia, as this may affect treatment options. A chest film is not required for the evaluation of asthma unless there are concerns for pneumonia or malignancy in the differential diagnosis of the patient's symptoms.

CASE ONE CONTINUED:

You review data from Mr. O'Brien's ED visit. His evaluation was notable for a white blood cell count of 7,000 with 10% eosinophils. The CXR from his ED visit had no acute findings.

You perform in-office spirometry on Mr. O'Brien during the visit with the following results:

		Pre-Bronchodilator		Post-Bronchodilator	
Test	**Actual**	**Predicted**	**% Predicted**	**Actual**	**% Change**
FVC (L)	**2.5**	**3.09**	**81**	**2.93**	**14**
FEV1 (L)	**1.64**	**2.57**	**64**	**2.13**	**30**
FEV1/FVC	**0.67**	**0.83**	**71**		**4**

3. **How do you interpret this patient's spirometry results?**
   There are three important measures from spirometry to pay attention to in patients with suspected asthma: functional vital capacity (FVC, maximum volume of air forcibly exhaled after maximal inhalation), forced expiratory volume (FEV1, maximum volume of air expired during first second of forced expiration), and the FEV1/FVC. Obstructive disease is marked by an FEV1/FVC less than predicted normal for age (typically 0.7 for adults). Patients with FEV1/FVC <0.7 are considered to have mild obstruction if FEV1 > 70% predicted, moderate obstruction if FEV1 is 50-69% predicted, and severe obstruction if FEV1 < 50% predicted. (Note, this is a statement about degree of obstruction, it is used as one factor in the classification of the severity of asthma [see below].)

   Patients with asthma typically have signs of reversible airway obstruction marked by a post-bronchodilator improvement in FEV1 by $\geq$200mL and $\geq$12% from baseline. Keep in mind that patients with intermittent and mild asthma may have normal spirometry results. These patients should undergo methacholine challenge to evaluate for inducible bronchoconstriction.

   Patients with severe asthma, as well as those with extensive tobacco use history, may lack reversibility of airway obstruction. Differentiating asthma from COPD in these patients can often be difficult by spirometry alone. Additional pulmonary function tests like diffusion capacity of carbon monoxide may be helpful to discern COPD/emphysema from asthma. Mr. O'Brien's spirometry results show a FEV1/FVC ratio of 0.67, suggesting presence of obstructive disease. His FEV1 of 64% suggests moderate obstruction. After bronchodilators,

his FEV1 improves by more than 0.2L and is >12% from baseline (this is 30% from baseline), suggesting he has reversible obstruction consistent with asthma.

4. **How would you classify this patient's asthma severity?**
A patient's asthma severity can be staged using the U.S. National Asthma Education and Prevention Program (NAEPP) approach (figure 2 of the JAMA article, reproduced below). The NAEPP evaluates asthma severity based upon level of asthma impairment and risk.

Asthma impairment is assessed based upon the severity of airway obstruction, frequency and intensity of daytime/nocturnal symptoms, frequency of rescue inhaler use, or amount of interference to daily activities caused by asthma symptoms. **Asthma risk** is measured by frequency of exacerbations within a one-year time frame requiring oral systemic steroids.

The "rule of 2s" is a simple mnemonic to differentiate intermittent asthma from mild persistent asthma based upon clinical history alone. Patients with intermittent asthma have SYMPTOMS $\leq$2 days per week, use RESCUE INHALERS $\leq$2 days per week, OR have NOCTURNAL AWAKENING $\leq$2 times a month. Moderate persistent asthma is differentiated from mild persistent asthma by DAILY symptoms or DAILY use of rescue inhalers, or WEEKLY nocturnal awakening. Patients who have symptoms throughout the day or require multiple doses of rescue inhalers a day typically have severe persistent asthma. Again, keep in mind that spirometry results should be taken into account as symptom-based evaluations of asthma alone are not always accurate.

Keep in mind that patients are classified based upon the highest NAEPP severity category that they match. Initial severity using this method is best assessed when patients are not on controller medications (see question 5). Re-classification of severity is made at subsequent visits based upon asthma control and pharmacotherapy treatment required.

Components of Severity		Classification of Asthma Severity (Youths ≥ 12 Years of Age and Adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 y 85% 20–39 y 80% 40–59 y 75% 60–80 y 70%	Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2x/month	3–4x/month	> 1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symtom control (not prevention of EIB)	≤ 2 days/week	> 2 days/week but not daily, and not more than 1x/day on any day	Daily	Several times per day
	Interference with normal activity	none	Minor limitation	Some limitation	Extremely limited
	Lung Function	• Normal FEV_1 between exacerbations • FEV_1 > 80% predicted • FEV_1/FVC normal	• FEV_1 ≥ 80% predicted • FEV_1/FVC normal	• FEV_1 > 60% but < 80% predicted • FEV_1/FVC reduced 5%	• FEV_1 < 60% predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥ 2/year (see note) →		
		← 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 FEV_1.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Source: NAEPP[2]

Mr. O'Brien has had nocturnal awakenings in the past week requiring albuterol rescue inhaler four times. His FEV1 is 64%. He meets criteria for moderate persistent asthma.

5. **What pharmacologic options are available in the treatment of asthma? Which would you start for this patient?**
Table 2 of the JAMA article provides a summary of the therapeutic classes, example generics, dosing, treatment effects, and adverse effects of medications used in the treatment of asthma.

To summarize, pharmacotherapy for asthma is categorized into "reliever" medications and "controller" medications. Reliever medications are short acting inhaled agents like ß2-agonists and oral corticosteroids.

Reliever Medication:

Short acting ß2-agonists (SABA) – SABAs (e.g., albuterol) are the first-line asthma reliever medications. Also called a "rescue" medication, SABAs should be taken two puffs every four to six hours as needed but can be used as frequently as two puffs every 20 minutes for over a one-hour time frame. All patients with asthma should have a prescription for a SABA. Patients with intermittent asthma typically do not require any other medication aside from their rescue inhaler.

Oral corticosteroids are typically reserved for asthma exacerbations that do not respond to first-line inhaled reliever medications, or for exacerbations with significant airway obstruction (see peak flow monitoring below). The typical dose of oral corticosteroids in adults is prednisone 40mg daily.

Controller Medication:

Controller medications for asthma include three types of inhaled medications: inhaled corticosteroids, long-acting ß2-agonists, long-acting muscarinic-antagonists and two oral medications: leukotriene receptor antagonists and leukotriene synthesis inhibitors.

Inhaled corticosteroids (ICS) **–** ICS (e.g., budesonide) have been shown to improve lung function, reduce symptoms, and hospital admissions due to exacerbations in patients with asthma. They can be prescribed in low, moderate, and high doses depending on the patient's asthma severity (see JAMA article). ICS are typically dosed twice daily. Patients should be counseled on appropriate oral hygiene, including rinsing the mouth after each use of inhaled ICS to prevent development of oral candidiasis. Any patient with persistent asthma should typically be on an inhaled corticosteroid.

Long acting ß2-agonists (LABA) – LABAs (e.g., salmeterol) are recommended for patients with moderate to severe persistent asthma and can increase airway caliber for up to 12-24 hours. LABAs should always be prescribed with an ICS. Studies have found that LABAs when prescribed without ICS have been associated with increased asthma hospitalizations, intubations, and mortality. From 2003-2017, all inhalers containing LABAs, including combination LABA-ICS inhalers, were required by the FDA to carry a black-box warning as a result. However, more recent studies have shown that patients on combination LABA-ICS treatment did not have increased risk of adverse effects. As of December 2017, the FDA has removed the black box warning required on combination LABA-ICS medications (Busse, 2018).

Long acting muscarinic-antagonists (LAMA) – While more typically used in the management of COPD, LAMAs (e.g., tiotropium) have been shown to improve FEV1 in patients with severe persistent asthma.

Leukotriene Inhibitors – Both leukotriene receptor antagonists (e.g., montelukast) and leukotriene synthesis inhibitors (e.g., zileuton) act on the pathways that contribute to airway smooth muscle contraction and eosinophilic inflammation. They can be used as an alternative to ICS in mild persistent asthma, or as an alternative to LABAs in moderate to severe persistent asthma.

The NAEPP has a step-wise approach to initiation of asthma therapy based upon the patient's asthma severity. See Figure 3 of the JAMA article.

Given that Mr. O'Brien has moderate persistent asthma, he should begin on step 3 therapy: low dose inhaled corticosteroid + long acting ß2-agonist. You prescribe him fluticasone-salmeterol (Advair) 100/50, one puff twice daily and refill his as-needed albuterol inhaler.

6. **What objective measures can be used to monitor asthma control in this patient?**
Peak flow measurements: Providers should teach patients how to use home peak flow measurements to self-monitor their asthma control. Peak flow meters (as cheap as $15/meter retail) are hand held devices that record expiratory volume and rate. Peak flow measurement is an effective surrogate marker of airway obstruction (utilization of peak flow measurements in home monitoring is described below in question 7).

Symptom-based questionnaires: Patients who have asthma that is not adequately controlled should return two to six weeks after medication changes for follow-up. Several validated in-office questionnaires are available, in addition to peak flow monitoring, to objectively quantify asthma control. These include the Asthma Control Test (ACT - https://www.asthma.com/additional-resources/asthma-control-test.html) and the Asthma Quality of Life questionnaire (AQOL - http://www.qoltech.co.uk/index.htm). These tools include score cutoffs for when to consider recommending step-up in asthma pharmacotherapy. If a patient's asthma is subsequently adequately controlled for three months, providers can consider step-down in pharmacotherapy.

Repeat spirometry: In general, repeat spirometry should be obtained every one to two years, and/or whenever there is a progressive decline in asthma control.

7. **What additional counseling would you provide this patient to improve his asthma management?**
Management of asthma requires a multi-modal approach, with pharmacotherapy comprising just one aspect of management. Patients should be counseled regarding inhaler technique and adherence, lifestyle/exposure modifications, as well as self-monitoring of asthma symptoms and control (Israel, 2017).

Inhaler technique/Adherence: Controller medication non-adherence and inappropriate inhaler technique are leading causes of uncontrolled asthma. Patients should be asked about the frequency with which they use each of their asthma medications at each visit. Patients often remember their inhalers by color rather than name. For a graphic to help patients identify their inhalers, including those used in COPD, please visit: https://www.samterssociety.org/inhalers.

Patients with poorly controlled asthma should be asked to demonstrate how they use their inhalers. Videos demonstrating appropriate inhaler technique can be found here: https://www.cdc.gov/asthma/inhaler_video/default.htm. Prescription of spacers and chamber devices ($10-$30) can improve effective delivery of aerosolized medications to the airways. Of note, studies have shown that when used correctly, rescue medications delivered

by metered dose inhalers are just as effective as nebulized formulations (Cates, 2013; Newman, 2002).

Lifestyle/exposure modifications: Patients should be counseled to avoid potential environmental exposures and triggers, such as tobacco use, exposure to second hand smoke, mold, and environmental allergens. Patients with seasonal allergies, rhinosinusitis, or GERD should receive treatment for these concomitant diseases that can worsen asthma symptoms.

Asthma Action Plans: All patients with asthma should have an asthma action plans. Sample asthma action plans can be downloaded from the NIH: https://www.nhlbi.nih.gov/files/docs/public/lung/asthma_actplan.pdf.

Asthma action plans allow patients to classify their asthma control into "zones" based upon symptoms and home peak flow readings. For those who do not have a "personal best" home peak flow value, estimated normal peak flow values based upon gender, age, and height can be found at http://www.asthma.partners.org/NewFiles/Appendix2.html.

Peak flow zones of green, yellow, and red can provide an early indication of uncontrolled asthma. Asthma action plans have been shown to reduce hospitalizations in children (Zemek, 2008); a Cochrane review of poor-quality studies did not show obvious benefit in adults (Gatheral, 2017).

If Mr. O'Brien's normal peak flow is estimated to be approximately 600 L/min a sample asthma action plan may look like the below:

- When peak flow is >80% (> 480L/min) of predicted peak flow or personal best, no changes to baseline controller medications need to be made (green zone)
- When peak flow is between 50-80% (between 300L/min and 480L/min) of predicted or personal best, he should continue his baseline controller medications, but increase the frequency of reliever medications to two puffs every 20 minutes for one hour (yellow zone)
- When peak flow is <50% (<300L/min) of predicted or personal best, he should increase frequency of reliever medications to two puffs every 20 minutes for one hour, start prednisone 40mg PO, and call his physician immediately (red zone)

CASE ONE CONTINUED:

You review the asthma inhaler technique with Mr. O'Brien and prescribe a spacer. You counsel him regarding smoking cessation, which he is willing to try, with the aid of nicotine replacement therapy. You also start him on loratadine 10mg daily for his allergy symptoms. You provide Mr. O'Brien with a copy of his asthma action plan and prescribe him a home peak flow meter.

Mr. O'Brien follows-up with you for his asthma on several occasions during the following year reporting persistent symptoms despite advancing him to high-dose ICS-LABA, adding tiotropium, and leukotriene receptor antagonists. He continues to have allergy symptoms as well.

8. **When should biologic agents for the treatment of asthma be considered?**
   Since 2003, several new biologic agents have been approved for the management of asthma. These agents target IgE and several mediators of the inflammatory cascade linked with eosinophilic inflammation in asthma. These include anti-IgE antibody omalizumab; anti-IL5 antibodies mepolizumab, reslizumab, and benralizumab. The anti-IL13 and anti-IL4 antibody dupilumab is currently in the pipeline for FDA approval. All agents are either subcutaneous or intravenous injections dosed monthly or twice monthly (Israel, 2017).

   A biologic agent should be considered in patients who have severe persistent asthma despite demonstrated adherence to controller medications and lifestyle modifications. Table 2 of the NEJM article by Israel summarizes the dosing, mechanism of action, target patient population, and benefits of individual biologic agents. To summarize, clinical indications that suggest potential benefit from biologic treatment include:

   Omalizumab: Patients with IgE levels > 30 IU/mL OR at least one positive aeroallergen skin test/elevated aeroallergen IgE level can be considered for omalizumab. During airway inflammation, increased levels of nitric oxide (NO) are released from epithelial cells of the bronchial wall. The fractional exhaled nitric oxide (FeNO), can help identify allergic/eosinophilic inflammation (Dweik, 2011). Elevations in the fraction of exhaled nitric oxide (FeNO) of $\geq$ 19.5ppb on pulmonary function testing further help identify patients who would experience a reduction in exacerbations by approximately 50% when started on omalizumab.

   Mepolizumab, reslizumab, benralizumab: Patients who have two or more exacerbations a year AND a serum eosinophil count $\geq$ 300/uL should be considered for these anti-IL5 antibodies.

   Dupilumab: Patients with elevated IgE levels and elevated FeNO (cutoffs not described) may benefit from dupilumab.

Use of biologic agents in patients with severe asthma has been shown to reduce exacerbations requiring hospitalization and symptoms but has not necessarily been associated with any effect on improving lung function in terms of FEV1 measurements.

CASE ONE CONTINUED:

Mr. O'Brien has severe persistent asthma despite adherence to treatment, in addition to an elevated peripheral eosinophil count and a history of atopy. He should have an IgE level checked, and also be referred to an allergy or asthma specialist for further evaluation and potential initiation of biologic agents.

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CME Questions:

1. **A 19-year-old gentleman presents to clinic with one year of intermittent non-productive cough, chest tightness, and wheezing occurring about once a month, particularly worse with exercise. His spirometry shows an FEV1/FVC of 0.83. What do you do next?**

    a. He does not have asthma
    b. Repeat spirometry after treatment with bronchodilator
    c. Perform methacholine challenge
    d. He has asthma, prescribe him albuterol

2. **A 50-year-old gentleman with asthma since childhood and ongoing 40-pack year smoking history presents to clinic for follow-up. He is prescribed fluticasone-salmeterol 250/50 one puff twice daily and rescue albuterol. In the last month, he has had daily symptoms requiring daily albuterol rescue inhaler use, sometimes more than once a day. He reports adherence to his inhalers and demonstrates appropriate technique. What is your next step?**

    a. Counsel on smoking cessation and increase dose of fluticasone-salmeterol
    b. Consider adding short course of corticosteroids
    c. Immediate referral to a pulmonologist
    d. a and b

3. **All of the following are potential indications for addition of biologic agents in the treatment of severe persistent asthma, except:**

    a. Elevated serum IgE levels
    b. More than two exacerbations of asthma in the previous 12 months
    c. Elevated serum eosinophil levels
    d. Elevated fractional excretion of nitrogen >19ppb

Answers:

1. **c** *This patient likely has mild intermittent exercise-induced asthma. Patients with mild-intermittent asthma –particularly those with exercise-induced asthma-- may not demonstrate obstructive pattern on spirometry and should be considered for methacholine challenge.*
2. **d** *This patient has severe persistent asthma based upon his current daily symptoms and more than daily albuterol use. His current prescriptions of moderate dose ICS-LABA and albuterol indicate a prior diagnosis of moderate persistent asthma. He should be advanced to step 4-5 of asthma treatment, indicating high dose ICS-LABA. This patient should also be considered for a short course of oral corticosteroids. Additional treatment options include addition of leukotriene inhibitors or long-acting muscarinic-antagonists. Because there is still room for treatment intensification, he does not require referral to pulmonologist at this time.*
3. **b** *Greater than two exacerbations of asthma in the previous 12 months alone without the additional serologic markers is not an indication for use of biologics in asthma.*