Asthma

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INTRODUCTION

Asthma is a treatable chronic inflammatory lung disease that appears to be increasing in prevalence in the United States and throughout the world. It is estimated that asthma affects approximately 15 million persons in the United States.[1] Asthma is the most common chronic disease in children, affecting 5.8% of patients younger than 18 years.[2] Children had close to 200,000 hospitalizations for asthma in 2002, mostly those younger than 5 years.[3] U.S. hospital admissions and deaths due to asthma are more common in African-American patients, tracking to a large degree with socioeconomic status.[4] It is important that physicians identify and adequately treat chronic asthma to avoid adverse outcomes.

CASE STUDY

INITIAL PRESENTATION

A 25-year-old woman presents to her primary care physician with the complaint that she is becoming more winded when she jogs in the morning.

HISTORY

The patient reports that she usually runs 3 to 5 miles most days of the week. Over the last several weeks, she finds that she becomes short of breath about 2 miles into the run. If she stops to walk, her breathing returns to normal but it takes about 5 or 6 minutes to do so. The sensation of dyspnea has been worse since the mornings have gotten colder.

The patient has never smoked. She has no past medical history other than eczema as a child. She never had trouble with her breathing before and played soccer through high school. She lives with 2 roommates, one of whom smokes. She works as a high school teacher. She received a cat for her birthday about 6 weeks ago.

PHYSICAL EXAMINATION

The patient is afebrile and in no distress. Her respiratory rate is 14 breaths/min, and her oxygen saturation on room air is 99%. She has no sinus tenderness and but does have nasal polyps. Pulmonary examination is notable for faint, scattered expiratory wheezes heard anterior and posteriorly. Cardiac examination is normal. She has no cyanosis, clubbing, or edema.

- **Which historical features indicate a possible diagnosis of asthma?**

The history given by the patient should raise the possibility of asthma as a cause of her dyspnea. Asthma is a chronic inflammatory lung disease characterized by episodes of increased airways inflammation resulting in airflow obstruction and dyspnea. In most patients, the predominant inflammatory cells involved include mast cells, T cells, and eosinophils[1,5]; however, in a subset of patients with asthma, a neutrophil-rich response is found. Patients with asthma have airways that demonstrate hyperresponsiveness to a variety of stimuli, becoming narrowed due to smooth muscle constriction, airway edema, and mucus production. The classic presenting symptoms of asthma include dyspnea, wheeze, and cough.

- **What is the clinical approach to making a diagnosis of asthma?**

DIAGNOSING ASTHMA

The first step diagnosing asthma involves taking a thorough history, with particular emphasis on potential triggers for a patient's dyspnea. As asthma is commonly associated with atopy (about 60% of patients), common allergens can be triggers as well as nonallergic stimuli such as exercise and viral upper respiratory tract infections. **Table 1** provides a more comprehensive list of triggers. Additional historical information that points toward a diagnosis of asthma includes a personal history of eczema, nasal polyps, seasonal allergies, or aspirin sensitivity. A family history of atopic disease also supports a diagnosis of asthma. In this patient, nasal polyps and a history of eczema are both present.

In this case, it seems the patient's symptoms are potentially triggered by exercise, as she notes worsening dyspnea with running. She may also be sensitive to cold air and cat dander, as her symptoms appear to have

worsened with the change in the weather and with the arrival of her new pet.

There is no single test that diagnoses asthma; however, all patients in whom asthma is suspected should undergo pulmonary function testing to assess for airways obstruction. For most patients, the best test is spirometry with bronchodilator testing. This study is used to assess for obstructive physiology (defined as force expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] < 70%) as well as responsiveness to bronchodilators. By American Thoracic Society (ATS) criteria, an improvement of 200 mL *and* 12% in either FEV_1 or FVC is considered an acute response to bronchodilators.[6] This pattern of reversibility is a hallmark of asthma; however, it is not diagnostic of asthma, as some patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis will also have a degree of reversibility. Additionally, a lack of response to bronchodilator testing does not preclude a clinical response to bronchodilator therapy and should not exclude a trial of a controller medication. As with COPD, the diagnosis of obstruction is made by demonstration of decreased FEV_1/FVC, while the severity of disease is evaluated by the FEV_1.

An alternate way to assess for airways obstruction is to measure peak expiratory flow with a hand-held peak flow meter. The results can be compared with average values for patients of similar age and height (**Table 2** and **Table 3**); however, there is wide variability in individual peak flows. Additionally, peak flow measurements are very effort dependent and require attentive patient education to obtain reliable results. Peak flow monitoring has a greater role in assessing control of asthma and creating action plans for patients. In general, initial spirometry is preferred for the diagnosis of asthma, although peak flow measurements are certainly less expensive and potentially more accessible than spirometry.

Many patients with less severe asthma will have normal spirometry when initially tested. There are 2 different options for further evaluation at this point. Patients with asthma, as previously discussed, have increased airways reactivity. One way to evaluate for this reactivity is with a provocative test aimed at causing bronchoconstriction, traditionally with a methacholine bronchoprovocation test. This study involves having a patient inhale progressively higher doses of methacholine (a muscarinic agonist which stimulates bronchial smooth muscle constriction) and repeating spirometry, assessing for changes in FEV_1. A decrement of 20% in FEV_1 is considered a positive test. The concentration of methacholine that causes this 20% fall in FEV_1 is termed a PC_{20}.[7] Some caution in interpreting methacholine provocation studies is warranted as other diseases, such as seasonal allergies and COPD,[8] can result in a false-positive methacholine challenge results. However, the negative predictive value is quite high (95% in 1 study)[9] when the prevalence in the population is low. Under these conditions, a negative test result virtually rules out asthma as the cause of the patient's symptoms. Although methacholine is the most common agent used for this test, in the appropriate clinical setting cold air and exercise can be used as provocative agents with similar measurements.[7] Exercise is mostly used when there is a question of exercise-induced asthma.

Table 1. Common Asthma Triggers

Viral infections
Animal dander (especially cats)
Cockroach excrement
Dust mites
Mold
Pollen
Exercise
Tobacco smoke
Perfume
Aspirin
Changes in temperature/humidity
Menses
Gastroesophageal reflux disease

An alternate strategy to further assess a patient with normal spirometry is to have the patient take peak expiratory flow measurements over a 2- to 3-week period and record them in a peak flow diary. Ideally, the patient measures peak flow at different times of day as well as when symptomatic and asymptomatic. Patients should be instructed to perform 3 peak flow measurements at a time and to record the best of the 3 efforts.[10] Often, the peak flow diary recording is performed after the health provider prescribes an "as needed" bronchodilator (usually a beta-agonist such as albuterol). In this situation, patients should take measurements before and after use of the medication. As discussed previously, peak flow measurements are very effort dependent and require patient education in order for results to be meaningful. Because of this, many pulmonologists prefer methacholine challenge and consider it to be the gold standard. However, peak flow testing is less expensive and often easier for a patient to complete.[11] Variability of 20% or more in peak flow measurements is consistent with a diagnosis of asthma.

It is important to remember the adage that "all that

Table 2. Predicted Peak Flows (L/min) for Normal Men

	Height, in				
Age, yr	**60**	**65**	**70**	**75**	**80**
20	554	602	649	693	740
25	543	590	636	679	725
30	532	577	622	664	710
35	521	565	609	651	695
40	509	552	596	636	680
45	498	540	583	622	665
50	486	527	569	607	649
55	475	515	556	593	634
60	463	502	542	578	618
65	452	490	529	564	603
70	440	477	515	550	587

Adapted with permission from Leiner GC, Abramowitz S, Small MJ, et al. Expiratory peak flow rate. Standard values for normal subjects. Use as a clinical test of ventilatory function. Am Rev Respir Dis 1963; 88:644–51.

Table 3. Predicted Peak Flows (L/min) for Normal Women

	Height, in				
Age, yr	**55**	**60**	**65**	**70**	**75**
20	390	423	460	496	529
25	385	418	454	490	523
30	380	413	448	483	516
35	375	408	442	476	509
40	370	402	436	470	502
45	365	397	430	464	495
50	360	391	424	457	488
55	355	386	418	451	482
60	350	380	412	445	475
65	345	375	406	439	468
70	340	369	400	432	461

Adapted with permission from Leiner GC, Abramowitz S, Small MJ, et al. Expiratory peak flow rate. Standard values for normal subjects. Use as a clinical test of ventilatory function. Am Rev Respir Dis 1963; 88:644–51.

wheezes is not asthma" and thoroughly evaluate for alternate etiologies when the diagnosis for asthma is not clear. Additional pulmonary function tests, including lung volume and diffusing capacity of the lung for carbon monoxide measurement, can reveal restrictive physiology or gas exchange impairments. Examination of the flow-volume loop can be informative as well. Flattening of the inspiratory loop suggests extrathoracic obstruction, such as vocal cord dysfunction or a neck mass compressing the trachea. Conversely, a plateaued expiratory limb warrants investigation for intrathoracic obstruction. Further studies could include a chest radiograph to assess for bronchiectasis or changes consistent with COPD. Some clinicians favor assessing for eosinophilia and elevated IgE levels, as these findings would support a diagnosis of asthma. However, these are not routine tests that should be ordered in all patients being assessed for a diagnosis of asthma. Patients with a monophonic wheeze or localized wheeze should be evaluated for a discrete bronchial obstruction that may be caused by a foreign body, an endobronchial tumor, or an extrinsic compressing mass.

In this patient, initial testing with spirometry with bronchodilator would be appropriate, particularly as she is currently wheezy on examination. There is a good chance that mild airways obstruction as well as a significant response to bronchodilators will be seen.

TESTING IN THIS PATIENT

The patient undergoes spirometry while in the office. Her results are shown below.

	Prebronchodilator	Postbronchodilator
FEV_1	3.75 L (82% predicted)	4.43 L (97% predicted)
FVC	4.90 L (94% predicted)	4.92 L (94% predicted)
FEV_1/FVC	76%	90%

While the results do not identify obstructive disease ($FEV_1/FVC > 70\%$), these pulmonary function tests reveal a significant bronchodilator response. Based on the history and spirometry findings, the physician diagnoses the patient with asthma.

On further questioning, the patient states that she notices the sensation of chest tightness at times when she is not exercising. She estimates this happens 2 or 3 times a week. She also notes that she is occasionally awakened from sleep with coughing but not more than once or twice a month.

- **How would you classify this patient's asthma?**

CLASSIFICATION OF DISEASE SEVERITY

Since the National Asthma Education and Prevention Program (NAEPP) first published its guidelines in 1991, patients with asthma have been divided into categories based predominantly on the frequency of their symptoms. Recommendations were guided by the classification of patients into the following categories: *mild intermittent*, *mild persistent*, *moderate persistent*, and *severe persistent*.[11] The most recent update of the NAEPP guidelines in 2002 used these same categories.[12] The description of each category and its specific symptom

Table 4. National Asthma Education and Prevention Program Step-wise Approach to Therapy

	Symptoms	Nighttime Symptoms	Lung Function
Step 4 Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	FEV_1 or PEF ≤ 60% PEF variability > 30%
Step 3 Moderate persistent	Daily symptoms Daily use of short-acting beta-agonist Exacerbations > 2× week Exacerbations affect activity	> 1 time/week	FEV_1 or PEF > 60% but < 80% predicted PEF variability > 30%
Step 2 Mild persistent	Symptoms > 2× week but < daily Exacerbations may affect activity	> 2× month	FEV_1 and PEF ≥ 80% predicted PEF variability 20%–30%
Step 1 Mild intermittent	Symptoms < 2× week Asymptomatic and normal PEF between exacerbations	≤ 2× month	FEV_1 and PEF ≥ 80% predicted PEF variability < 20%

FEV_1 = forced expiration volume in 1 second; PEF = peak expiratory flow. (Adapted from National Asthma Education and Prevention Program expert panel report guidelines for the diagnosis and management of asthma–update on selected topics 2002. Bethesda [MD]: US Dept. of Health and Human Services, National Institutes of Health, and the National Heart, Lung, and Blood Institute; 2002 Jun. NIH Publication No. 02-5075. Available at www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf. Accessed 20 Jul 2007.)

Table 5. Levels of Asthma Control

Characteristic	Controlled (all of the following)	Partly Controlled (and measure present in any week)	Uncontrolled
Daytime symptoms	None (≤ 2 times per week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (≤ 2 doses per week)	More than twice/week	
Lung function (PEF or FEV_1)	Normal	< 80% of predicted or personal best (if known)	
Exacerbations	None	1 or more/year	One in any week

FEV_1 = forced expiration volume in 1 second; PEF = peak expiratory flow. (Adapted with permission from the Global Initiative for Asthma [GINA]. Global strategy for asthma management and prevention, 2006. Available at www.ginasthma.org. Accessed 20 Jul 2007.)

and lung function criteria are included in **Table 4**. The classification of a patient's asthma guides therapy in step-wise fashion, stepping down when control is adequate and stepping up when a patient has persistent symptoms.

While the severity of symptoms is still a part of the classification of a patient's asthma, there has been a new emphasis on grading the severity of asthma based on degree of control. The Global Initiative for Asthma (GINA) (**Table 5**) favors the following categories: *controlled*, *partly controlled*, and *uncontrolled*.[1] In contrast, the new NAEPP proposed guidelines divide symptoms into intermittent or persistent and then grade the severity of symptoms using the traditional mild, moderate, and severe categories. As these recommendations are not yet formalized, they have not been included. However, new NAEPP guidelines should be released within the year.

The patient presented in this case would be classified as having mild persistent asthma (by NAEPP guidelines) or partly controlled asthma (GINA). For all patients who have more than mild intermittent asthma, a controller medication is recommended as a first step in therapy.

- **What therapy should be initiated in this patient?**

TREATMENT

As has already been mentioned, asthma is best treated in a step-wise fashion, with initial treatment aimed at full control of symptoms and then progressive stepping down of therapy as possible. If adequate control is not achieved, then a patient's therapy is ramped up to try to fully control symptoms.

Mild Intermittent Asthma

For patients who have intermittent symptoms that occur fewer than 2 times a week and have no nocturnal symptoms, the recommended treatment is a short-acting bronchodilator to be used on an as-needed

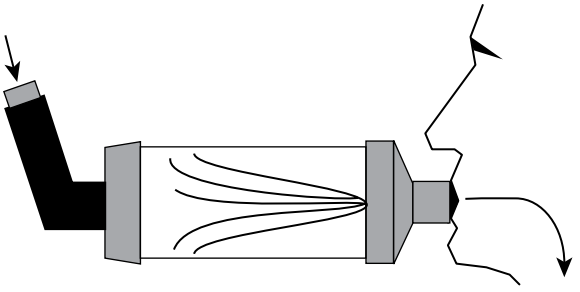

Figure. Depicts a multidose inhaler (*in black*) attached to a spacer device. The patient squeezes the inhaler to administer a dose. In the spacer, the medication is broken into smaller particles, increasing the likelihood of delivery of the medication to the lower airways and avoiding deposition in the posterior oropharynx. Many spacer devices also have a whistling sound that indicates that the patient is inhaling too quickly.

basis.[11] The most commonly used medication is albuterol, a short-acting beta-agonist. All metered-dose inhalers (MDIs) should be used with a spacer (**Figure**), which helps create smaller particles of drug that are better delivered to the distal airways and less likely to be deposited in the posterior oropharynx.[13]

Alternately, patients can be treated with cromolyn or nedocromolyn (most commonly in exercise-induced asthma). However, these medications only work to prevent symptoms and do not have rapid-onset bronchodilating effects like albuterol. There remains debate about whether patients with intermittent asthma should be treated with a controller medication targeted at the underlying inflammation in asthma.[14] At this time, there are no data that support the use of steroid inhalers or leukotriene inhibitors in intermittent asthma.

It should be noted that patients with only exercise-induced asthma should be categorized as "intermittent" even if their symptoms are more frequent than twice weekly. These patients generally benefit from short-acting bronchodilator treatment 10 to 15 minutes prior to exercise.[15] If using a short-acting bronchodilator does not prevent symptoms, a controller medication should be considered.

Mild Persistent Asthma

Patients with more persistent asthma should be treated with a controller medication that targets the underlying inflammatory nature of asthma. For most patients, the first-line agent is either a low- or moderate-dose inhaled steroid. Several studies have demonstrated improved symptom control and quality of life as well as a decrease in exacerbations with regular treatment with a steroid inhaler.[16–18] There are several options for steroid inhalers (**Table 6**), most of which are administered on a twice daily basis with the exception of budesonide and mometasone, which are available in a once-daily dosing formulation.

Table 6. Common Steroid Inhaler Preparations

Medication	Doses Available	Low Dosage	High Dosage
Beclomethasone	42 μg/puff	4–12 puffs daily	> 20 puffs daily
	84 μg/puff	2–6 puffs daily	> 10 puffs daily
Bedesonide (dry powder)	200 μg/puff	1–2 puffs daily	> 3 puffs daily
Fluticasone*	44 μg/puff	2–6 puffs daily	
	110 μg/puff	2 puffs daily	> 6 puffs daily
	220 μg/puff		> 3 puffs daily
Triamcinolone	100 μg/puff	4–10 puffs	> 20 puffs

*Also available as a dry powder inhaler with slightly different dosages.

The most common side effect with steroid inhalers is thrush. Thrush can be avoided for the most part by having patients use a spacer and rinse their mouth after using the inhaler. Dry powder inhalers are increasingly available and do not require spacers. Moderate-dose steroids have little systemic absorption, although this varies from patient to patient. Systemic absorption occurs with higher-dose steroids, and patients who take higher-dose steroids are at risk for cataracts, decreased bone density, and suppression of the hypothalamic-pituitary axis.[19–21]

A reasonable alternative to a steroid inhaler as an initial controller medication is a leukotriene-modifying agent. There are 2 categories that are currently available. The first is leukotriene receptor antagonists, specifically zafirlukast and montelukast. These medications act by modifying the leukotriene pathway, which contributes to the smooth muscle constriction and mucus secretion seen in asthma. Additionally, a 5-lipoxygenase inhibitor (zileuton) is also available for treating asthma. It also affects the leukotriene pathway resulting in decreased inflammation and airways reactivity. As this medication is dosed 4 times daily, there can be issues of patient compliance with zileuton. Leukotriene modifiers have been shown to improve lung function, decrease use of beta-agonists, and improve quality of life.[22,23] While some patients have a dramatic response to therapy with leukotriene modifiers, many patients do not and fewer patients respond to leukotriene modifiers than to inhaled corticosteroids. At this time, there are no good predictors of who will respond to leukotriene modifiers, so an empiric trial of a given medication for 2 to 3 weeks makes sense. One

subcategory of patients who do seem to gain benefit from leukotriene modifiers are those with asthma and aspirin sensitivity.[24] Other markers of response remain to be determined. There are few side effects associated with leukotriene inhibitors, with the most common adverse reaction being gastrointestinal upset. When these medications were first introduced, there appeared to be an increased incidence of Churg-Strauss syndrome in patients initiating leukotriene modifiers. Most clinicians now believe that this was a phenomenon related to tapering corticosteroids and revealing preexisting Churg-Strauss syndrome.[25] Further studies are needed to fully understand this relationship.

Guidelines also suggest that theophylline is an acceptable alternative for treatment of mild persistent asthma, although most clinicians do not initiate therapy with this medication. Theophylline, a phosphodiesterase inhibitor, has clear bronchodilator effects; however, it also has a narrow therapeutic window, making it more difficult to administer this agent without adverse effects. The major side effects include palpitations, insomnia, and gastrointestinal upset.

All patients with asthma should also have a "rescue" medication to be used in the setting of acute exacerbations of symptoms. Usually, a short-acting beta-agonist such as albuterol is prescribed.

Moderate Persistent Asthma

Patients who have more frequent symptoms, during the day or at night, or worse pulmonary function are classified as having moderate persistent asthma.[11] Perhaps more commonly, the patient who appears to have mild persistent asthma but who is not well controlled with a moderate-dose steroid inhaler should be classified as having moderate persistent asthma. In this setting, therapy needs to be stepped up. There are a few options for additional therapy.

Traditionally, most physicians added a long-acting beta-agonist (LABA), specifically salmeterol, to a steroid inhaler for patients who needed further therapy. This adjustment was made easier in the last few years with the introduction of combined steroid/LABA inhalers. Studies have shown that patients have decreased symptoms and decreased use of short-acting beta-agonist with the addition of a LABA in contrast to increasing the dose of steroid inhaler.[26,27] In the last few years, there has been evidence that patients treated with LABA alone have an increased mortality.[28] It appears that this risk is most prominent in African-American patients with asthma.[29] These findings have resulted in a black box warning on salmeterol. Because of this, some clinicians are hesitant to initiate LABA even with a steroid inhaler while others continue to use the combined medications. Patients with asthma should not be treated with a long-acting bronchodilator alone.

An alternative to the addition of LABA is to increase the dose of steroid inhaler to a high-dose steroid inhaler. The downside of this approach is that patients taking high-dose steroid inhalers have increased systemic absorption of the medication and are at greater risk of the side effects of steroids. Another option is to add a leukotriene modifier to a steroid inhaler in this situation. As discussed previously, a minority of patients respond to leukotriene modifiers, but for certain patients this combination can achieve excellent control. This combination has been shown to decrease symptoms and improve peak flows.[30,31]

Severe Persistent Asthma

Patients who continue to have symptoms despite stepping up therapy or who have severe impairment of pulmonary function or activity are categorized as severe persistent. These patients warrant referral to a pulmonologist for assessment and treatment. Additional therapies, including systemic steroids and anti-IgE therapy, are considered in these special cases. Also, a more comprehensive assessment for alternative diagnoses and persistent triggers should be undertaken. Further discussion of the care of patients with severe persistent asthma is beyond the scope of this article.

INITIAL MANAGEMENT

The patient has mild persistent asthma that is not currently well controlled. The physician prescribes a moderate-dose steroid inhaler, fluticasone 110 μg twice daily, and teaches her proper inhaler technique. The patient is instructed to rinse her mouth after each use of the inhaler. While in the office, the physician gives her a peak flow meter and teaches her how to use it. She is asked to check her peak flows throughout the day and keep track of them in the diary the physician provides. She asks why she needs to perform peak flow measurement. She also asks if there is anything else she needs to do in order to stay healthy.

- **What are the key elements of patient education in asthma therapy?**

Action Plan

Each patient with asthma should have an action plan, focusing on early responses to changes in pulmonary function.[11] Most action plans are based on peak flow measurements. Initially, patients need to establish a personal best peak expiratory flow by measuring over

Table 7. Asthma Action Plan

Color	PEF (% Personal Best)	Response
Green	80–100	No change in therapy
Yellow	50–80	Contact physician
Red	< 50	Urgent visit/emergency department

PEF = peak expiratory flow.

several days. Most patients have their best values in the afternoon or early evening. Once a baseline has been established, an action plan can be developed based on percentages of personal best.

When patient's values are within 80% of personal best, the patient needs no change in therapy. This is often called the green zone. When peak flows fall to between 50% and 80% of personal best (yellow zone), patients are encouraged to contact their physician for guidance on adjustment of medications. Patients should recognize that when peak flows fall below 50% of baseline (red zone), they need to seek medical attention urgently. A traditional action plan structure is outlined in **Table 7**.

Environmental Management

Essential for good asthma control is avoidance or minimization of triggers. Patients who are sensitive to dust mites should be taught about the use of pillow covers and should launder bedding on a weekly basis.[32] Specific allergens should be avoided if at all possible. For many patients, this means staying indoors and using air conditioning during times of high pollen counts. If the patient is sensitive to cat dander, cats need to be removed from the house or at least limited to outside of the bedroom. Homes should be cleaned regularly, although often the process of cleaning can trigger a patient's asthma, requiring someone other than the patient to clean the house.[32] Aggressive measures to remove cockroaches should be employed.[33] Finally, if a patient knows that she is going to be exposed to an allergen, pretreatment with a short-acting bronchodilator is recommended.

CASE CONTINUED

Several months later, the patient calls the office because she cannot seem to recover from a recent cold. She reports increased shortness of breath and a sensation that her chest is tighter than usual. She also notes that her peak flows have fallen into the yellow zone on her action plan. She also states that she has been using her albuterol inhaler 4 to 5 times per day for the last few days, but it does not seem to be helping as much as it did.

- **What is the most appropriate management at this time?**

MANAGEMENT OF AN ACUTE ASTHMA EXACERBATION

Definition and Severity of an Acute Exacerbation

This patient demonstrates many of the findings associated with an acute exacerbation of asthma. Symptoms such as increased cough, wheeze, or dyspnea can indicate an exacerbation, particularly when associated with a known trigger such as an allergen exposure or an upper respiratory tract infection. Other common features include increased use of short-acting bronchodilators, nocturnal awakenings, and increased early morning symptoms. Objective measurement of peak flows helps not only to diagnose a flare but also to grade the severity.

Generally, when peak flows have fallen below 80% of personal best but remain above 50%, the exacerbation is considered mild to moderate. In this setting, it is reasonable for the patient to follow the established action plan and then contact their physician based on initial response to therapy. Most significantly, if a patient has a good response to increased dosing of albuterol (eg, 2–4 puffs every 20 minutes for an hour), including relief of symptoms and improvement in peak flow, it is reasonable to continue with the action plan and contact the physician within 48 hours.[11] However, a less robust response to initial therapy warrants contacting a health care provider more urgently. If peak flows fall below 50% of a patient's personal best, the exacerbation is considered severe and a patient should be counseled to seek medical attention immediately as well as initiate medications included in the action plan.

Pharmacologic Therapy

The cornerstones of medical therapy for acute exacerbations of asthma are short-acting bronchodilators and corticosteroids.

Bronchodilators. The first step in treating an asthma flare is to administer additional beta-agonists, usually albuterol. Almost all action plans will have patients increase the use of albuterol inhalers at home as a first step in therapy. The NAEEP guidelines recommend the use of 2 to 4 puffs by MDI at 20-minute intervals for an hour or a single nebulized treatment.[11] There is evidence that albuterol can be administered either via MDI (with spacer) or nebulizer with good effect, although there is probably better delivery of medication with the MDI/spacer.[34] That being said, many

patients find it easier to use a nebulizer when in mild to moderate distress, and this route generally requires less coaching of the patient. For this reason, many emergency departments routinely administer nebulized medications in the acute setting; however, either route is appropriate.

In patients who do not achieve significant relief with albuterol treatment, many providers add inhaled ipratropium therapy. The data for the use of this medication are conflicting, with some studies showing no benefit to the combination of medications[35] and 2 meta-analyses supporting the use of anticholinergic therapy in patients with severe disease.[36,37] For the most part, asthma action plans do not include the initiation of ipratropium, as it is generally added to the regimen of a patient who is not responding to increasing doses of albuterol and manifesting signs of a severe flare.

Corticosteroids. Asthma flares that do not significantly respond to treatment with increased dosing of bronchodilators require therapy with corticosteroids. For the most part, patients should receive systemic corticosteroids, although in mild exacerbations it may be reasonable to increase a patient's dose of inhaled corticosteroid for 7 to 10 days. There is no convincing evidence that this actually decreases the use of oral steroids; however, it may be a reasonable option in selected patients and is included in the NAEEP guidelines.[11,38] This is an option in patients who peak flow returns to greater than 80% of their personal best with initial increased dosing of albuterol.

If a patient has not had a significant response to increased bronchodilators with a marked improvement in symptoms and peak flow, systemic corticosteroids should be initiated without delay. As these medications usually take at least 4 to 6 hours to begin to demonstrate an anti-inflammatory effect, the sooner they are administered the more rapidly a patient will begin to improve. Studies have shown that systemic steroids improve the rate of improvement and decrease the likelihood of recurrent exacerbation.[39,40] A common starting dose of prednisone is 60 mg, although there are no data to guide this dose choice. There is also no convincing evidence that there is additional benefit to administering corticosteroids intravenously as opposed to orally, although many institutions follow this practice.[41] Most patients do well with a 7- to 14-day course of corticosteroids, with more severe exacerbations usually requiring the longer end of the spectrum. While commonly tapered, it is not clear that this is needed for such short courses of steroids.

Other therapies. Many other therapies have been used in the treatment of acute exacerbations of asthma. For the most part, these therapies are considered in patients who are refractory to beta-agonists and steroids. While the evidence is mixed, magnesium may have a role in treating severe, resistant bronchospasm but should not be considered as part of standard therapy for an asthma exacerbation.[42] The usual dose is 2 g administered over 20 minutes.

Neither methylxanthines (theophylline and aminophylline) nor empiric antibiotics have been shown to improve outcomes for patients with acute exacerbations of asthma.[43,44] For this reason, neither medication is recommended by the NAEEP or GINA for treatment of the patient with an asthma flare.[1,11] Interestingly, there is some evidence of improved symptoms in patients treated with macrolide antibiotics, regardless of the patient's bacteriologic status. The role of these agents, potentially as anti-inflammatory medications, remains to be fully elucidated, and they are not currently recommended for routine care.[45] Finally, helium–oxygen mixtures (heliox) have been used to treat severe asthma exacerbations based on the theory that the lower density gas results in greater laminar airflow and improves gas movement through severely obstructed airways. Meta-analyses have not shown benefit for nonintubated patients treated with heliox.[46] Small, uncontrolled studies have shown change in physiologic parameters in patients with refractory severe obstruction and those with respiratory failure.[47,48] Once again, neither GINA nor NAEEP recommend heliox as part of standard therapy for acute exacerbations of asthma.[1,11]

Severe Exacerbations

Approximately 4000 people die each year from asthma exacerbations.[49] Thus, clinicians need to be alert for early clinical findings suggestive of a severe flare. In addition to dramatically decreased peak flow measurements, other concerning findings include use of accessory muscles, inability to complete a full sentence, inability to lay flat, or frank respiratory distress. The finding of a pulsus paradoxus, or fall in systolic blood pressure by more than 12 mm Hg with inspiration, is also a marker of severity.[50] Most patients, even those with very severe exacerbations, will not become hypoxemic, so clinicians should not be falsely reassured by a normal pulse oximetry when assessing a patient.

In contrast, it is more common for patients with severe obstruction to develop hypercarbia as opposed to hypoxemia. Hypercarbia is best assessed by an arterial blood gas, although this is generally only indicated when there is evidence of marked obstruction. Early in an exacerbation, patients may have lower than expected P_{CO_2} levels. Because of this, as patients begin

to tire, it is common to first see a "normal" P_{CO_2} level. Once again, this should not always be a reassuring finding and close monitoring is indicated.

Patients who have a history of asthma exacerbations requiring intubation are at increased risk of death from their asthma.[51] It is not clear that these patients' asthma is different pathophysiologically, but it does appear that there is a subset of patients who are slower to respond to therapy. These patients are at greater risk of developing severe, refractory airway obstruction, often termed *status asthmaticus,* as well as respiratory failure. As there is no easy way to predict which patients fall into this category, early vigilance for signs of fatigue and progressive hypercarbia are essential in all patients with severe exacerbations. Early intubation should be considered in any patient with evidence of impending respiratory failure. Further discussion of the ventilation and critical care management of these patients is outside the scope of this article.

SUMMARY

- Asthma is a chronic inflammatory lung disease characterized by reversible airflow limitation. Patients typically present with wheeze, dyspnea, and cough.
- Diagnosis of asthma should include a consistent history, including specific triggers of symptoms, as well as objective measurement of airways obstruction by spirometry or peak expiratory flow measurement.
- Management of asthma is based on step-wise therapy, increasing medications to obtain control and then deescalating medications as feasible.
- All patients should have an action plan, usually based on peak expiratory flow, and know when to seek immediate medical attention.
- Environmental controls are essential in the effective control of asthma symptoms.

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