Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

Mild Asthma

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A 26-year-old graduate student with an eight-year history of asthma has shortness of breath and cough an average of three times a week and nighttime wheezing about twice a month. He is an avid runner and wheezes routinely after exercise. Office spirometry shows that the forced expiratory volume in one second (FEV_1) is 85 percent of the predicted value. What treatment should be recommended?

The Clinical Problem

The treatment of mild asthma raises fundamental management issues. The use of substantial doses of controller therapy (e.g., inhaled corticosteroids) is well accepted for the treatment of moderate or severe asthma, but the role of these therapies is controversial in milder disease. If inhaled corticosteroids had no side effects, the current evidence indicating that airway inflammation is present even in mild intermittent asthma[1,2] would suggest their use in all patients with asthma. However, the continuous use of these medications can be expensive and may be associated with side effects such as thrush and dysphonia. Some investigators have also voiced concern about the long-term effects of corticosteroids on growth and bone mineralization as well as the risk of early cataract formation.[3] The treatment of mild asthma must therefore balance the potential benefits and possible risks of therapy.

Definition of Mild Asthma

The National Asthma Education and Prevention Program (NAEPP) defines asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. . . . In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment."[4] The severity of asthma has been classified by the NAEPP[4] and the Global Initiative for Asthma.[5] The classifications use both objective measures of lung function and the frequency of clinical symptoms to gauge the severity of asthma. Concern has been voiced about the lack of validation of these classifications,[6] but studies confirm that the findings of such an approach correlate with other markers of airway inflammation.[2,7]

In the NAEPP guidelines,[4] mild persistent asthma is defined by the occurrence of daytime symptoms less than once a day and more than twice a month, nocturnal awakenings less than twice a week, and an FEV_1 that is at least 80 percent of the predicted value (Table 1). Patients with mild intermittent asthma have symptoms even less frequently, no more than twice a week during the day or twice a month at night. An objective spirometric evaluation of lung function is essential, even in patients who are thought to have mild asthma, because some patients who have few symptoms may nonetheless have moderate or severe airflow obstruction on spirometry.[8,9] Such patients are classified as having moderate persistent and severe persistent asthma, respectively. The physical examination has a poor ability to determine the severity of airflow obstruction.[10]

Strategies and Evidence

Treatment of Mild Intermittent Asthma

Patient Education and Monitoring

Although this discussion will focus on therapy, the importance of patient education cannot be overemphasized. Since patients with mild disease can still have exacerbations, they must know how to recognize and manage these flares and to identify and, if possible, avoid environmental triggers. To understand the roles of their medications, patients need basic information about the pathophysiology of asthma. This approach is especially important in patients with mild disease, because they become asymptomatic with successful treatment and may not adhere to treatment regimens once their symptoms resolve.

Patients should have scheduled follow-up appointments at least every six months, independent of visits for acute exacerbations, to reinforce management strategies and to reassess the severity of asthma.[4] The assessment should include both a review of the patient's clinical history, with special attention to nighttime symptoms, and objective measurements, preferably spirometry; without objective monitoring, patients who

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TABLE 1. CLASSIFICATION OF THE SEVERITY OF ASTHMA.*

SEVERITY OF ASTHMA	CLINICAL FEATURES BEFORE TREATMENT†	NIGHTTIME SYMPTOMS	LUNG FUNCTION
Severe persistent asthma	Continual symptoms Physical activity limited Frequent exacerbations	Frequent	FEV_1 or PEF ≤60% of predicted value Variability in PEF >30%
Moderate persistent asthma	Daily symptoms Daily use of inhaled β_2-agonists Activity affected by exacerbations Exacerbations >2 times/wk	>1 time/wk	FEV_1 or PEF 61–79% of predicted value Variability in PEF >30%
Mild persistent asthma	Symptoms >2 times/wk but <1 time/day Activity may be affected by exacerbations	>2 times/mo	FEV_1 or PEF ≥80% of predicted value Variability in PEF 20–30%
Mild intermittent asthma	Symptoms ≤2 times/wk No symptoms and normal level of activity between exacerbations Exacerbations brief	≤2 times/mo	FEV_1 or PEF ≥80% of predicted value Variability in PEF <20%

*Data are from the National Asthma Education and Prevention Program.[4] Patients with asthma of any severity can have mild, moderate, or severe exacerbations separated by long periods of normal lung function and no symptoms. FEV_1 denotes forced expiratory volume in one second, and PEF peak expiratory flow.

†The presence of any one feature is sufficient to place a patient in that category. A patient should be classified as having the most severe grade in which any feature occurs. The characteristics given for each category are general and may overlap, because asthma is highly variable. Furthermore, a patient's classification may change over time.

have moderate or even severe disease may be misclassified. A peak-flow assessment (with the results compared with the patient's own best value) is less sensitive than spirometry to changes in airway obstruction but is better than no objective measurement at all.

The role of peak-flow meters in self-assessment in patients with mild disease is controversial. Although peak-flow meters might seem helpful, clinical studies have not confirmed that their use in such patients provides a long-term advantage.[11] The NAEPP guidelines no longer recommend routine peak-flow monitoring in patients with mild intermittent or mild persistent disease. Regardless of whether routine peak-flow monitoring is used, all patients should receive individualized, written plans of action that explain what to do in the event of exacerbation.

β_2-Agonists

Short-acting inhaled β_2-agonists such as albuterol or terbutaline are highly effective for the quick relief of acute bronchospasm and are the treatment of choice for patients with mild intermittent asthma. Debate over regularly scheduled as compared with as-needed use of albuterol is largely moot in this context, since the infrequent nature of symptoms does not warrant continuous therapy. Early reports[12,13] suggested that the scheduled use of albuterol was associated with poorer control of asthma. However, a more recent study conducted by the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network demonstrated little difference between the two strategies in patients with mild asthma.[14] The use of albuterol in response to symptoms has a practical advantage over scheduled use, in that an increasing need for albuterol may signal the onset of an acute exacerbation or may reveal to the patient and practitioner that the control of asthma is gradually worsening and that the institution of long-term controlling therapy is required.

Treatment of Mild Persistent Asthma

Inhaled Corticosteroids

Since mild asthma, by definition, is associated with normal or nearly normal base-line lung function, an incremental benefit from long-term antiinflammatory therapy would accrue if it accomplished one or more of the following: reduced the frequency or severity of exacerbations, reduced the acute response to stimuli such as exercise or allergens, or slowed the long-term loss of lung function (which declines more quickly over time in those with asthma than in those without asthma[15]). As summarized below, controller therapy, such as inhaled corticosteroids, can have a substantial effect on acute exacerbations and symptoms, but whether the use of inhaled corticosteroids can alter the natural history of asthma is unknown.

Most, but not all, investigators agree that controller therapy is indicated for mild persistent asthma. Haahtela et al.[16] treated patients with asthma with either high-dose budesonide (1200 μg per day) or terbutaline and found that patients who received inhaled corticosteroids had better lung function, as assessed by the FEV_1, and better control of symptoms than those who received terbutaline. Subsequently, the patients who had received high-dose budesonide were treated with low-dose inhaled budesonide (400 μg per day) or placebo, and those who had received terbutaline were given high-dose inhaled budesonide.[17] Symptoms remained under control in the majority

(74 percent) of patients who were taking low-dose inhaled corticosteroids but returned in most patients (67 percent) who were receiving placebo. It is noteworthy that patients who received terbutaline alone during the first two years of the study had some improvement in FEV_1 during the subsequent course of high-dose budesonide therapy, but not to the extent observed in the patients who had first received high-dose inhaled corticosteroids.

The Childhood Asthma Management Program Research Group investigated the effect of four to six years of therapy on lung growth and function in children by comparing low-dose inhaled budesonide (400 μg per day) with either nedocromil sodium or placebo in a double-blind, randomized trial.[18] Budesonide treatment resulted in a higher FEV_1 than did placebo at one year, but no significant differences in lung function were evident among the drug groups and the placebo group after four years of treatment.[18] There was an effect on height at one year but not in later years. The group treated with budesonide clearly had better control of symptoms and fewer exacerbations than did either the placebo or the nedocromil group.

Nedocromil and Cromolyn Sodium

Nedocromil and cromolyn sodium have few side effects and have been proposed as alternative therapies for mild asthma. Schwartz et al.[19] studied 306 patients with mild-to-moderate disease and found that those receiving nedocromil had improvements in symptoms, pulmonary function, and the need for rescue medication, as compared with those receiving cromolyn or placebo. Long-term nedocromil therapy was also studied in the Childhood Asthma Management Program trial.[18] Treatment with this agent produced no long-term difference in lung function when compared with placebo, nor did it prevent exacerbations or acute symptoms as well as did budesonide.

Agents That Modify the Leukotriene Pathway

Agents that modify the leukotriene pathway, either by antagonizing the receptor for leukotriene D_4 (such as montelukast, pranlukast, and zafirlukast) or by inhibiting the 5-lipoxygenase enzyme involved in their synthesis (such as zileuton), can reduce airway inflammation and decrease asthma symptoms, as reviewed recently in the *Journal*.[20] However, there have been no long-term (longer than six months) randomized, controlled trials to compare the effects of these medications with those of inhaled corticosteroids on airway remodeling or lung function. The few industry-sponsored, shorter-term trials to date have demonstrated an improvement with the use of both inhaled corticosteroids and leukotriene-pathway–modifying drugs. The short-term improvement in FEV_1 was greater in patients who received inhaled corticosteroids.[21,22] The response to leukotriene-pathway modifiers varies considerably among patients. However, patients with aspirin-sensitive asthma may benefit particularly from this class of drugs.[20]

Treatment of Asthma Induced by Cold Air and Exercise

Exercise-induced symptoms can occur in patients with asthma of any severity. Exercise in dry, cold, or

TABLE 2. RECOMMENDATIONS REGARDING MILD ASTHMA.*

TYPE OF ASTHMA	LONG-TERM CONTROL	QUICK RELIEF OR PRETREATMENT	EDUCATION
Mild intermittent	No daily medication is needed.	Short-acting inhaled β_2-agonists should be taken as needed for symptoms.†	Patients should be taught basic asthma facts, how to use an inhaler or spacer, when to use medications, and how to avoid environmental triggers. A self-management plan should be devised that includes a plan of action for exacerbations.
Mild persistent	One daily medication is needed, with low-dose inhaled corticosteroids and cromolyn or nedocromil sodium (in children) as the first choice and low-dose theophylline or a leukotriene modifier.	Short-acting inhaled β_2-agonists should be taken as needed for symptoms.†	Patients should be taught all the items listed above as well as how to monitor their condition. Patients should be referred to group education if available. The self-management plan should be reviewed and updated.
Exercise-induced	Inhaled corticosteroids are recommended.	Short-acting inhaled β_2-agonists or cromolyn sodium should be taken before exercise.	Teachers and coaches of children with asthma should be notified. Competitive athletes should be told of the U.S. Olympic Committee's standards for medication use.

*Data are adapted from the National Asthma Education and Prevention Program.[4]

†Daily use of short-acting inhaled β_2-agonists indicates the need for additional therapy.

even temperate environments leads to cooling and drying of the airways, thereby generating a potent stimulus for bronchoconstriction.[23] This same mechanism may also cause bronchoconstriction in patients exposed to cold air in the absence of exercise. Exercise-induced symptoms are usually maximal in the 5 to 10 minutes after activity stops.

A traditional approach to the treatment of asthma induced by cold air and exercise is pretreatment with an inhaled β_2-agonist or a cromone (cromolyn or nedocromil).[24] Newer drug therapies may eliminate the need for pretreatment. Long-term treatment with inhaled corticosteroids reduces exercise-induced bronchoconstriction.[25] Patients with mild asthma treated with 10 mg of montelukast per day for 12 weeks also had less severe bronchoconstriction after exercise.[26] Salmeterol can attenuate bronchoconstriction in patients with asthma who are exercising in cold air,[27] but with prolonged treatment, the duration of protection diminishes and is gone within nine hours. Thus, with long-term use, salmeterol must be taken close to the time of exercise, somewhat reducing its advantage over pretreatment with albuterol.

In a placebo-controlled, head-to-head comparison of salmeterol with montelukast, zafirlukast, and zileuton, all drugs ameliorated the fall in FEV_1 induced

TABLE 3. USUAL DOSES OF MEDICATIONS USED FOR THE LONG-TERM CONTROL OF MILD PERSISTENT ASTHMA.*

DRUG	ADULT DOSE	DOSE IN CHILDREN >5 YR	COMMENTS
Inhaled low-dose corticosteroids			
Beclomethasone with CFC propellant			
Total dose	168–504 μg/day	84–336 μg/day	
42 μg/inhalation	4–12 inhalations/day	2–8 inhalations/day	
84 μg/inhalation	2–6 inhalations/day	1–4 inhalations/day	
Beclomethasone with HFA propellant			
Total dose	160–480 μg/day	80–320 μg/day	
40 μg/inhalation	4–12 inhalations/day	2–8 inhalations/day	
80 μg/inhalation	2–6 inhalations/day	1–4 inhalations/day	
Budesonide			
Total dose	200–400 μg/day	200 μg/day	
200 μg/dose (DPI)	1–2 inhalations/day	1 inhalation/day	
Flunisolide			
Total dose	500–1000 μg/day	500–750 μg/day	
250 μg/inhalation	2–4 inhalations/day	2–5 inhalations/day	
Fluticasone			
Total dose	88–264 μg/day	88–176 μg/day	
44 μg/inhalation (metered-dose inhaler)	2–6 inhalations/day	2–4 inhalations/day	
88 μg/inhalation (metered-dose inhaler)	2 inhalations/day		
50 μg/inhalation (DPI)	2–6 inhalations/day	2–4 inhalations/day	
Triamcinolone acetonide			
Total dose	400–1000 μg/day	400–800 μg/day	
100 μg/inhalation	4–10 inhalations/day	4–8 inhalations/day	
Other agents			
Cromolyn sodium	6–16 inhalations/day	3–12 inhalations/day	One dose should be given before exercise.
Nedocromil sodium	4–16 inhalations/day	2–8 inhalations/day	
Theophylline	10 mg/kg of body weight/day initially	16 mg/kg/day initially	Serum levels should be adjusted to 5 to 15 μg/ml and monitored.
Zileuton	600 mg orally 4 times daily		Alanine aminotransferase levels should be monitored.
Montelukast	10 mg orally at bedtime	5 mg orally at bedtime	Possible relation to the Churg–Strauss syndrome.
Zafirlukast	20 mg orally twice daily		Hepatotoxicity occurs in rare instances; possible relation to the Churg–Strauss syndrome.

*Data are from the National Asthma Education and Prevention Program.[4] CFC denotes chlorofluorocarbon, HFA hydrofluoroalkane, and DPI dry-powder inhaler.

by exercise in cold air.[28] Only a single dose of each drug was administered, so their long-term therapeutic benefits could not be compared. A similar comparison showed that budesonide provided greater protection than montelukast against exercise-induced bronchoconstriction, but the response to therapy with either agent varied among subjects.[29] Ultimately, drug selection for exercise-induced bronchospasm should depend on the patient's preferences and the presence or absence of persistent symptoms.

AREAS OF UNCERTAINTY

The potential role of leukotriene-pathway–modifying agents as long-term monotherapy needs to be clarified.

GUIDELINES

The NAEPP guidelines,[4] summarized in Tables 2 and 3, recommend inhaled corticosteroids for long-term treatment of mild persistent asthma, although alternative medications are also mentioned. The guidelines stress the importance of patient education, written plans of action, and follow-up visits that include objective measurement of lung function by spirometry.

CONCLUSIONS AND RECOMMENDATIONS

Our own recommendations are similar to those of the NAEPP guidelines. Patients with mild intermittent asthma are the only group that can be treated with beta-agonists alone. These patients must receive education and twice-yearly follow-up visits that include an objective assessment of lung function to detect subtle worsening that mandates the initiation of controller therapy. Worsening severity is indicated by an increase in the frequency of symptoms to more than twice a week, an increase in the frequency of nighttime symptoms to more than twice a month, or a deterioration in lung function.

The patient in the case vignette is best described as having mild persistent asthma. We would initiate therapy with a low dose of an inhaled corticosteroid. If his exercise-induced symptoms persisted, we would advise him to take albuterol before exercise. In general, leukotriene-receptor antagonists, such as montelukast and zafirlukast, remain an attractive alternative for patients with mild persistent asthma, although in our experience the response to this therapy is quite variable. These agents may also be helpful in patients who refuse to take inhaled corticosteroids or in those few who are unable to use inhalation therapy. Cromolones remain an option for patients with clear allergic triggers, but nedocromil fared less well than an inhaled corticosteroid in long-term trials in children with mild asthma. Although theophylline is listed as an alternative for mild persistent asthma in the NAEPP guidelines, we view it as a second-line agent reserved for more severe disease, owing to its potential toxicity and monitoring requirements.

Patients with mild persistent asthma should have follow-up spirometry every six months. The occurrence of daily symptoms, nighttime symptoms more than once a week, or an FEV_1 that is less than 80 percent of the predicted value would prompt an escalation of therapy.

In the case of patients with exercise-induced asthma, the intensity of therapy should be matched to the severity of symptoms and the patients' expectations. For patients with mild symptoms, pretreatment with short-acting β_2-agonists, cromolyn, or nedocromil may be sufficient. Patients with more severe symptoms or those who are training competitively may require more sustained control with an inhaled corticosteroid or a leukotriene-receptor antagonist (for patients who have a response to this therapy). We do not advocate the use of salmeterol as monotherapy, because its degree of protection against exercise-induced bronchospasm appears to diminish with continued use and it could mask worsening inflammation. Salmeterol may be useful as a pretreatment before exercise in situations in which more prolonged bronchodilation is required, such as during periods of extended exercise.

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