

## CLINICAL PRACTICE

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## Mild Asthma

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*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 author's clinical recommendations.*

**A 20-year-old college student with a history of asthma and allergic rhinitis, which were diagnosed in childhood, presents with cough and tightness of the chest that interfere with his sleep three or four times per month. He requires albuterol two or three times per week. He enjoys playing tennis but generally wheezes after a match. Last year, during the pollen season, he sought treatment in an emergency department for acute asthma but was not admitted to the hospital. His forced expiratory volume in 1 second (FEV<sub>1</sub>) is 93% of the predicted value. How should this case be evaluated and managed?**

## THE CLINICAL PROBLEM

Asthma is a chronic inflammatory disease of the airways that is characterized by variable narrowing of the airways and symptoms of intermittent dyspnea, wheezing, and nighttime or early-morning coughing. Asthma is a major health problem throughout the world, affecting an estimated 315 million persons of all ages.<sup>1</sup> The prevalence of asthma varies widely among countries, ranging from 2% in Vietnam to 27% in Australia.<sup>1</sup> Asthma occurs more frequently in adults than in children and more frequently in boys than in girls; however, after the teenage years, asthma occurs more frequently in women than in men.<sup>2</sup>

Asthma is clinically heterogeneous, and its pathophysiology is complex.<sup>3</sup> Airway eosinophilic inflammation is typical, but many patients with mild asthma have persistently noneosinophilic disease.<sup>4</sup> Airway hyperresponsiveness is a consistent feature; irreversible airflow obstruction develops in some patients, presumably as a consequence of remodeling of the airway wall.<sup>3</sup> Short periods of loss of asthma control may occur as a result of exposure to nonspecific “triggers,” such as fumes, strong smells, or exercise. Moderate or severe exacerbations are usually due to exposure to allergens or viruses, particularly human rhinovirus.<sup>5</sup>

The development of asthma in children is influenced by genetic predisposition as well as by environmental factors, including viral infection and sensitization to aeroallergens (e.g., house dust mites or animal dander).<sup>6</sup> Altered repair responses of the airway epithelium to these insults lead to inflamed airways, altered smooth-muscle function, and increased production of mucus.<sup>3</sup> Persons who are born and raised on a farm have a reduced risk of allergy and asthma, probably because they have been exposed to a wide variety of microorganisms.<sup>7</sup> Risk factors for the development of asthma in middle-aged and older adults are diverse and include work-related exposures (e.g., isocyanates or cleaning products) and lifestyle factors (e.g., smoking or obesity).<sup>8,9</sup>

## NATURAL HISTORY

The natural history of asthma varies considerably according to the age of the patient at the first onset of symptoms, the severity of the asthma, and the patient's

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## KEY CLINICAL POINTS

**CONTROL OF ASTHMA**

- Most patients with asthma have mild, persistent disease, which tends to be underdiagnosed, undertreated, and inadequately controlled.
- The diagnosis of asthma is based on the presence of symptoms of dyspnea, cough, and wheezing and objective confirmation of variable airflow limitation that is at least partially reversible.
- For mild, persistent asthma, regular controller treatment with low-dose inhaled glucocorticoids and rescue treatment with short-acting beta<sub>2</sub>-agonists, as needed, is recommended as the initial treatment.
- If asthma control is not achieved within 3 to 4 months, maintenance treatment should be stepped up with the addition of a second controller medication (long-acting beta<sub>2</sub>-agonist or leukotriene modifier) or with an increase in the dose of inhaled glucocorticoids.
- Ongoing patient education, written action plans, and regular follow-up visits to reassess asthma control and adjust therapy are integral to successful management.

sex.<sup>8</sup> Mild asthma in children rarely progresses to severe disease, but severe and frequent wheezing is a well-established risk factor for persistence and severity of the disease in adulthood. Boys with asthma are more likely to “grow out” of their asthma, whereas asthma in girls is more likely to persist. Irreversible airflow limitation develops in some patients, particularly in those who have severe exacerbations.<sup>10</sup>

**SEVERITY AND CONTROL OF ASTHMA**

The clinical spectrum of asthma ranges from mild, intermittent symptoms to severe, refractory disease with frequent exacerbations, but the majority of patients with asthma have mild disease.<sup>11</sup> Without treatment, these patients have symptoms less than once a day, nighttime sleep disturbances less than once a week, sporadic exacerbations requiring treatment with oral glucocorticoids, and normal lung function between asthma episodes.<sup>12,13</sup> Because many patients with mild asthma do not seek care for their symptoms, mild asthma tends to be underdiagnosed, undertreated, and inadequately controlled.<sup>14</sup>

International expert panels have agreed that achievement and maintenance of good control should be the cornerstone of asthma management.<sup>12,13</sup> Asthma control involves the control of symptoms and functional impairments, as well as the reduction of the risk of future adverse events (e.g., asthma exacerbations, adverse effects of medications, and decline in lung function).<sup>15</sup> A classification of asthma severity that is based on

the intensity of the treatment required to achieve good asthma control has been proposed,<sup>16</sup> although it has not been universally accepted.<sup>13</sup> According to this classification, “mild” asthma refers to asthma that can be well controlled with low-intensity treatment, regardless of the severity of symptoms and airflow obstruction at presentation.

## STRATEGIES AND EVIDENCE

**EVALUATION**

The diagnosis of asthma is based on the presence of typical symptoms and on objective confirmation of variable airflow limitation that is at least partially reversible.<sup>12,13</sup> The assessment includes a detailed history and physical examination. Wheezing on auscultation suggests asthma, but that finding may be absent during quiet respiration or may be audible only during forced expiration or after exercise. Spirometry or measurement of peak expiratory flow provides an assessment of the severity of airflow limitation, its variability, and its reversibility (Table 1).<sup>12,13</sup> For patients with normal lung function, a negative bronchoprovocation test with inhaled methacholine or a negative test during exercise may be useful for ruling out asthma. Skin testing or *in vitro* testing is recommended to identify indoor allergens that may contribute to asthma symptoms in patients with relevant exposures.

Once a diagnosis of asthma is made, the level of asthma control should be assessed. Standard-

ized assessments such as the Asthma Control Questionnaire and the Asthma Control Test (see Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) have been shown to be valid and reliable tools in clinical practice for distinguishing between asthma that is well controlled and asthma that is not well controlled.<sup>17</sup>

#### PATIENT EDUCATION

Patients and health care professionals should discuss and agree on the goals of treatment and develop an individualized action plan. A review of randomized trials of written action plans showed that plans that based the action point on the patient's personal best peak expiratory flow (e.g., action taken when a 15% to 30% decrement is noted), and that included instructions for recognizing early signs of worsening asthma and taking action in case of an exacerbation (including recommendations for the use of inhaled and oral glucocorticoid therapy), resulted in reduced hospitalizations for asthma.<sup>18</sup> Ongoing patient education and regularly scheduled follow-up visits to reassess asthma control, adjust therapy, and promote adherence to medication are crucial for long-term success.

#### AVOIDANCE OF TRIGGERS

Relevant triggers that have been shown to aggravate asthma should be addressed and removed if possible. Exposure to aeroallergens has been convincingly shown to worsen asthma control in sensitized patients,<sup>19</sup> but there is conflicting evidence about whether measures to reduce exposure to dust mites and pet dander, the most common indoor allergen sources, lead to better asthma outcomes. Randomized trials of single chemical or physical methods that are aimed at reducing dust-mite allergens, for example, have shown no significant effect on asthma symptoms.<sup>20</sup> In addition, the clinical effectiveness of removing pets from the home remains unproven. However, multicomponent home-based interventions that target multiple triggers have been shown to reduce asthma symptoms and asthma-related utilization of health care resources.<sup>21</sup>

Exposure to tobacco smoke increases the severity of asthma in children and adolescents,<sup>22</sup> and active smoking reduces the response to asthma medication<sup>23</sup> and causes long-term impairment of lung function.<sup>24</sup> Smoke-free policies have been

**Table 1. Criteria for the Diagnosis of Asthma.\***

Presence of episodic symptoms of airflow obstruction or airway hyperresponsiveness
Objective assessment consisting of one of the following
Airflow obstruction that is at least partially reversible with the use of an inhaled short-acting beta <sub>2</sub> -agonist, as shown by one of three variables
An increase in FEV <sub>1</sub> of ≥12% from baseline
An increase in predicted FEV <sub>1</sub> of ≥10 percentage points from baseline
An increase in PEF of ≥20% (or 60 liters/min) from baseline
Diurnal variation in PEF (measured twice daily) of more than 10%

\* FEV<sub>1</sub> denotes forced expiratory volume in 1 second, and PEF peak expiratory flow.

associated with a reduction in emergency hospitalizations for asthma.<sup>25</sup> Smoking cessation is therefore strongly recommended for all patients with asthma and their caregivers who smoke.

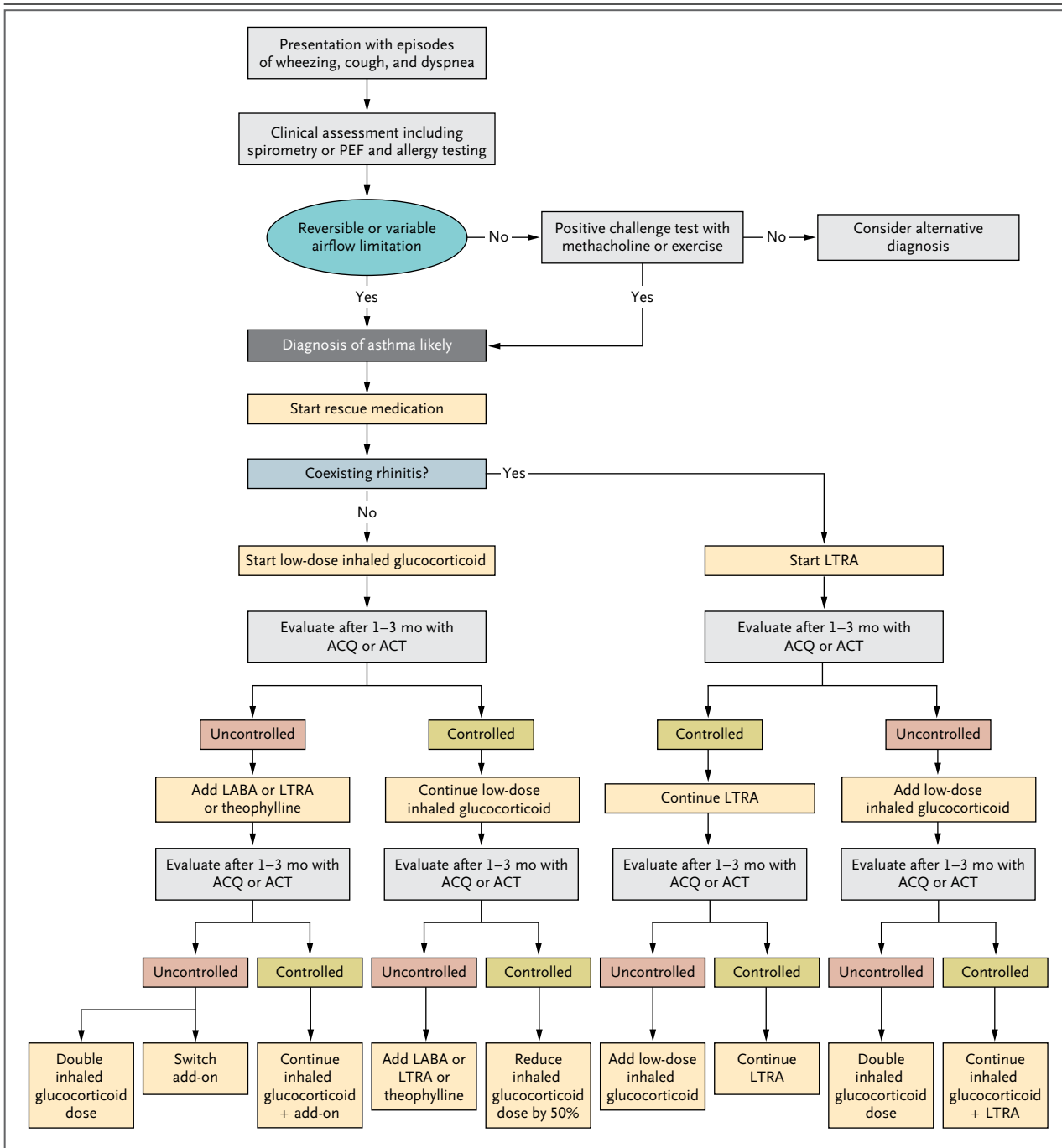
Coexisting conditions such as rhinitis and obesity may aggravate asthma symptoms, and treatment of these conditions in patients with asthma reduces asthma symptoms and improves lung function.<sup>26</sup> Gastroesophageal reflux is also common in patients with uncontrolled asthma; however, in a large, randomized, controlled trial, treatment with proton-pump inhibitors did not result in better asthma control.<sup>27</sup>

#### ASTHMA MEDICATIONS

The goal of asthma treatment is to achieve long-term clinical control while minimizing the side effects of treatment. Current guidelines recommend a stepwise approach to pharmacologic treatment,<sup>12,13</sup> in which treatment is initiated and adjusted (higher or lower) on the basis of ongoing assessments of the patient's level of asthma control (Fig. 1).

Asthma medications are classified into two categories: medications for long-term control, which are taken on a regular basis to achieve and maintain control of persistent asthma, and quick-relief medications that are used infrequently, when needed, to treat acute symptoms and exacerbations. Most asthma medications are administered through an inhaler, either a metered-dose inhaler with a spacer or a dry-powder inhaler.

For patients with mild, persistent asthma who



**Figure 1. Algorithm for the Treatment of Mild Asthma in Adults and Children Older Than 5 Years of Age.**

This algorithm is based largely on guidelines from the Global Initiative for Asthma<sup>12</sup> and the National Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute.<sup>13</sup> ACQ denotes Asthma Control Questionnaire, ACT Asthma Control Test, LABA long-acting beta<sub>2</sub>-agonist, LTRA leukotriene-receptor antagonist, and PEF peak expiratory flow.

have not received previous treatment, current guidelines recommend as the initial treatment a regular controller medication with a rescue medication as needed (Table 2). Rapid-acting inhaled beta<sub>2</sub>-agonists are the rescue medications of choice and should be taken as needed to reverse bronchoconstriction and relieve symptoms.<sup>28</sup> Although short-acting inhaled anticholinergic agents

**Table 2. Controller and Rescue Medications for the Treatment of Mild Asthma.\***

Indication and Drug	Children 6–11 Yr		Children ≥12 Yr and Adults		Side Effects
	Initial Daily Dose	Maximum Step-up Dose	Initial Daily Dose	Maximum Step-up Dose	
<b>Medications for quick relief</b>					
Short-acting beta <sub>2</sub> -agonists†					
Albuterol	200 µg, as needed	200 µg, six times a day‡	200 µg, as needed	200 µg, six times a day‡	Tachycardia, tremor, cough, headache
Terbutaline§	—	—	250 µg, as needed	500 µg, eight times a day‡	
Anticholinergic agent: ipratropium bromide¶					
	40 µg, as needed	40 µg, four times a day	40 µg, as needed	40 µg, six times a day	Dry mouth, headache, nausea
<b>Medications for long-term control</b>					
Inhaled glucocorticoids†					
Beclomethasone	50 µg, twice a day	200 µg, twice a day	50 µg, twice a day	200 µg, twice a day	Hoarseness, oral candidiasis, growth retardation (approximately 1 cm), glaucoma, agitation, hypersensitivity
Budesonide	100 µg, once a day	200 µg, twice a day	100 µg, twice a day	400 µg, twice a day	
Fluticasone	50 µg, twice a day	250 µg, twice a day	50 µg, twice a day	250 µg, twice a day	
Ciclesonide	—	—	80 µg, once a day	160 µg, twice a day	
Leukotriene modifier: oral montelukast					
	5 mg, once a day	5 mg, once a day	5 mg, once a day	10 mg, once a day	Sinusitis, abdominal pain, headache
Cromones					
Sodium cromoglycate					
	5 mg, four times a day	10 mg, four times a day	10 mg, four times a day	10 mg, eight times a day	Cough, bronchospasm
Nedocromil sodium					
	2 mg, four times a day	4 mg, four times a day	2 mg, four times a day	4 mg, four times a day	Headache, nausea
<b>Step-up or add-on medications</b>					
Long-acting beta <sub>2</sub> -agonists†					
Salmeterol	—	50 µg, twice a day	—	50 µg, twice a day	Tachycardia, tremor, headache, asthma exacerbations
Formoterol	—	12 µg, twice a day	—	24 µg, twice a day	
Oral theophylline					
	—	10 mg/kg, twice a day	—	5 mg/kg, twice a day	Reflux, headache, insomnia, tremor, tachycardia

\* All drug doses are approximate doses and apply to metered-dose inhalers unless specified otherwise.

† This is a preferred therapy.

‡ Daily use of rescue medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.

§ Terbutaline Turbuhaler is not available in the United States.

¶ Anticholinergic agents can be used as second-line therapy after therapy with short-acting beta<sub>2</sub>-agonists but do not have approval by the Food and Drug Administration for use in treatment of asthma. However, in many European countries, ipratropium bromide is approved for the treatment of asthma.

|| Montelukast can also be used as a step-up medication with inhaled glucocorticoids. Pranlukast or zafirlukast can be substituted for montelukast in adults; doses vary according to medication type.

are not approved by the Food and Drug Administration (FDA) for this indication, they may be used as alternative, albeit less effective, bronchodilators in patients who have unacceptable side effects with beta<sub>2</sub>-agonists.<sup>12,13</sup> (Ipratropium bromide, a commonly used anticholinergic agent, has never been considered for centralized approval by the European Medicines Agency; however, it is approved for the treatment of asthma in many European countries.)

For the long-term control of asthma, inhaled glucocorticoids are the most potent and consistently effective medications for achieving overall treatment goals.<sup>29</sup> These drugs are therefore the preferred therapy for patients with persistent asthma, including those who have generally well-controlled asthma but have had two or more asthma exacerbations requiring oral glucocorticoid therapy in the previous year.<sup>12,13</sup> Constant low-dose inhaled glucocorticoid therapy<sup>12,13</sup> has been shown in randomized, placebo-controlled trials to reduce asthma symptoms, improve asthma control and quality of life, improve lung function, diminish airway hyperresponsiveness, control airway inflammation, and reduce the frequency and severity of exacerbations.<sup>29,30</sup> A large, nested, case-control study showed that persons who regularly used low-dose inhaled glucocorticoids had a reduced risk of death from asthma.<sup>31</sup> Current evidence does not support the assumption that in children, early intervention with an inhaled glucocorticoid may alter the underlying severity or progression of the disease.<sup>32</sup> Inhaled glucocorticoids do not cure asthma, and when they are discontinued, asthma control deteriorates in weeks to months in roughly half the patients.<sup>33</sup>

Inhaled glucocorticoids at low doses, even when taken for extended periods of time, are generally considered to be safe.<sup>34</sup> Local side effects include dysphonia and oral candidiasis, which may be reduced by rinsing the mouth and spitting after inhalation, using a spacer device, or using extra-fine particle formulations that reduce oropharyngeal deposition.<sup>35</sup> Inhaled glucocorticoids are absorbed from the lung into the bloodstream and may cause systemic side effects in susceptible patients; a follow-up assessment of children who were enrolled in a placebo-controlled, randomized trial of inhaled glucocorticoid treatment showed a decrement of 1.2 cm, on average, in final height with long-term treatment.<sup>36</sup>

These medications should be adjusted to the lowest dose that is effective in maintaining good asthma control (see Table S1 in the Supplementary Appendix).

Over the past few years, the importance of regular glucocorticoid treatment for patients with mild asthma, as suggested by asthma treatment guidelines, has been challenged. A randomized, controlled trial involving adults suggested that intermittent short courses of inhaled glucocorticoids at the onset of asthma exacerbations have effects similar to those obtained with the regular use of inhaled glucocorticoids with respect to various measures of asthma control. However, not all drugs were similar, and some provided more improvement with daily therapy.<sup>37</sup> A recent meta-analysis of four trials involving pediatric patients and two trials involving adult patients showed that daily use of inhaled glucocorticoids is modestly superior to intermittent use with respect to good asthma control, reduction in airway inflammation, improvement in lung function, and reduction in the need for rescue medication.<sup>34</sup> Physicians and patients should consider the risks and benefits of each treatment option.

Leukotriene modifiers are alternative medications for the long-term control of asthma.<sup>38</sup> These drugs are particularly appropriate for patients who have concomitant allergic rhinitis<sup>39</sup> or who have unacceptable local side effects with inhaled glucocorticoid therapy or an inadequate response to inhaled glucocorticoids.<sup>40</sup> Large, randomized trials comparing leukotriene-modifier therapy with low-dose inhaled glucocorticoids in adults and children with mild, persistent asthma have shown that as compared with leukotriene-modifier therapy, inhaled glucocorticoid therapy results in significantly greater improvements with respect to most measures of asthma control.<sup>41</sup> However, two large pragmatic trials performed in community settings showed that leukotriene-receptor antagonists were similar in efficacy to inhaled glucocorticoids as first-line controller therapy.<sup>42</sup>

Other options such as theophylline and cromones (nedocromil sodium and sodium cromoglycate) are available, but these drugs are less effective than inhaled glucocorticoids or leukotriene modifiers as initial controller medications for mild, persistent asthma and are therefore not preferred therapies.<sup>12,13</sup>



**SPECIFIC IMMUNOTHERAPY**

Although specific immunotherapy has been shown to be effective in reducing asthma symptoms and airway hyperresponsiveness in patients with a single, well-defined, clinically relevant allergy,<sup>43</sup> the effect of this approach as compared with other treatment options is relatively modest. Specific immunotherapy should therefore be considered only when there is a substantial allergic contribution to a patient's symptoms, and pharmacologic intervention and avoidance of environmental allergens have failed to control the asthma.<sup>12,13</sup>

**MONITORING AND ADJUSTMENT OF THERAPY**

Once asthma control has been achieved, ongoing monitoring is essential to maintain control and to establish the lowest effective dose of treatment. Inhaler technique should be reviewed regularly (see the video in Hendeles et al.,<sup>44</sup> also available with this article, at NEJM.org), and patients should be queried regarding side effects of the medication. Avoidance of triggers and adherence to the medication should be discussed routinely. If the monitoring of peak expiratory flow is included in the written asthma action plan, the patient's personal best peak expiratory flow should be used as the reference value.<sup>18</sup>

In case of an anticipated brief loss of control (e.g., due to short-term exposure to an allergen), quadrupling the dose of inhaled glucocorticoids for 5 to 10 days might be an effective strategy for preventing progression to a severe exacerbation.<sup>37</sup> If lack of control persists for prolonged periods of time (2 to 3 weeks), maintenance treatment should be stepped up with the addition of a second controller medication (a long-acting beta<sub>2</sub>-agonist or a leukotriene modifier) or with an increase in the dose of inhaled glucocorticoids.<sup>45</sup> Randomized, controlled trials have shown that in adults, the addition of a long-acting bronchodilator to inhaled glucocorticoids leads to greater improvement in lung function and quality of life than the addition of a leukotriene-receptor antagonist.<sup>46</sup> However, large, randomized, double-blind clinical trials have suggested that long-acting bronchodilators may be associated with increased risks of serious asthma exacerbations and asthma-related deaths.<sup>47</sup> Therefore, the FDA now advises against using long-acting beta-agonists in patients whose asthma is adequately controlled with low-dose or medium-dose inhaled glucocorticoids.<sup>48</sup> In

addition, some patients have a better response to the addition of a leukotriene-receptor antagonist.<sup>46</sup>

**AREAS OF UNCERTAINTY**

Single-inhaler combination therapy, consisting of an inhaled glucocorticoid and a long-acting beta<sub>2</sub>-agonist, is increasingly being used for the treatment of patients with moderate asthma.<sup>49</sup> Whether this strategy is effective and safe in patients with mild asthma remains to be investigated.

When adequate control of asthma is maintained at a low dose of inhaled glucocorticoids for 3 to 4 months, guidelines recommend stepping down therapy. Proposed step-down strategies include a switch to intermittent use of inhaled glucocorticoids,<sup>33</sup> regular use of a leukotriene-receptor antagonist, or once-daily single-inhaler combination therapy with a glucocorticoid and a long-acting beta<sub>2</sub>-agonist.<sup>50</sup> However, the most appropriate step-down strategy remains uncertain.

Better strategies are needed for diagnosing and classifying asthma and for guiding asthma treatment. The use of biomarkers such as sputum eosinophil counts and exhaled nitric oxide levels has been suggested to aid in the assessment of asthma control, but the role of these biomarkers in clinical practice remains uncertain.<sup>51</sup>

Severe asthma exacerbations can occur even in patients with mild asthma that is well controlled,<sup>5</sup> with the exacerbations most often provoked by viral infections. Since inhaled glucocorticoids do not fully regulate virus-associated exacerbations, other (preventive) strategies are needed.<sup>5</sup>

**GUIDELINES**

The Global Initiative for Asthma (GINA)<sup>12</sup> and the National Asthma Education and Prevention Program (NAEPP) of the National Heart, Lung, and Blood Institute,<sup>13</sup> among other groups, have published guidelines on the evaluation and management of asthma. The recommendations in this review are generally consistent with the GINA and NAEPP guidelines.

**CONCLUSIONS AND RECOMMENDATIONS**

The patient described in the vignette has symptoms indicative of mild, persistent asthma. The



*A video showing the use of an albuterol metered-dose inhaler is available at NEJM.org*

frequency of daytime and nighttime symptoms and impairment with exercise suggest inadequate control. Before initiating daily controller treatment, I would confirm the diagnosis of asthma by means of spirometry or, in the absence of reversibility, by means of a challenge test with inhaled methacholine. I would also evaluate the patient's sensitization and exposure to allergens and educate him regarding strategies for good control of asthma, including a written action plan. In accordance with current guidelines, I would initiate treatment with regular low-dose inhaled glucocorticoids and a short-acting beta<sub>2</sub>-agonist as needed for rescue use. If after 3 to 4 months the response to treatment is unsatisfactory (as assessed with the use of a questionnaire such as

the Asthma Control Test), I would increase the dose of inhaled glucocorticoids or add a second controller medication. Long-acting beta<sub>2</sub>-agonists are the preferred therapy to add, but given his atopy and exercise-induced symptoms, a leukotriene-receptor antagonist would be a good alternative. If, however, he has a good response to low-dose inhaled glucocorticoids at follow-up, I would reduce the dose of inhaled glucocorticoids to the lowest possible dose required to maintain asthma control.

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