CLINICAL PRACTICE

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Asthma in Adults

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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 47-year-old woman with a history of asthma, which has been treated with daily low-dose inhaled glucocorticoids and a short-acting β_2-agonist (SABA) as needed, presents for a follow-up visit. She reports having shortness of breath 4 days per week when she is outdoors watching her daughter's soccer matches. Over the past year, she has had asthma exacerbations resulting in treatment with oral glucocorticoids in the spring and fall. How should this patient be evaluated and her care managed?

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THE CLINICAL PROBLEM

The prevalence of asthma in adults in the United States is approximately 7.7%.[1] It is one of the most common chronic, noncommunicable diseases in the country and worldwide.[1,2] Among U.S. adults, asthma disproportionately affects women, persons who are Black or Puerto Rican, and persons with low household income.[1] Although overall asthma-related mortality in the United States has decreased from 15.1 per million in 2001 to 9.9 per million in 2017,[3] the incidence of death due to asthma in the United States remains consistently higher among Black and Puerto Rican persons than among White persons.[4] In addition, although severe asthma affects 5 to 10% of all patients with asthma, it accounts for over 50% of asthma-related costs.[5,6]

The National Asthma Education and Prevention Program Expert Panel-3 Report defines asthma as "a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation" and notes that "[t]he interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment."[7] This article focuses on treatment advances for mild-to-moderate asthma.[7-10] The approach to treatment should be decided on the basis of a confirmed diagnosis of asthma that includes findings of variable airflow obstruction on spirometry.

The typical symptoms of asthma are also symptoms of other respiratory and nonrespiratory conditions.[7,8] Chronic cough, in the presence of normal lung function and a normal chest radiograph, should prompt consideration of allergic and nonallergic rhinitis, rhinosinusitis, nasal polyposis, gastroesophageal reflux disease, postviral tussive syndrome, chronic bronchitis, eosinophilic bronchitis, and cough induced by an angiotensin-converting enzyme inhibitor. If a patient presents with chronic wheeze, the differential diagnosis includes vocal-cord dysfunction, bronchiectasis, chronic obstructive pulmonary disease, bronchogenic carcinoma, and foreign-body aspiration. Common causes of shortness of breath that may be con-

KEY CLINICAL POINTS

ASTHMA IN ADULTS

- Asthma guidelines state that a definitive diagnosis of asthma should be based on the presence of characteristic respiratory symptoms such as wheeze, cough, chest tightness and shortness of breath, and variable expiratory airflow obstruction on spirometry.
- The three main goals of asthma management are control of symptoms, reduction in risk of exacerbations, and minimization of adverse effects of medications.
- Every visit should include a review of inhaler technique, medication adherence, coexisting conditions, ongoing exposures to environmental triggers, and confirmation of a correct diagnosis of asthma.
- In patients with mild asthma, the preferred treatment option is an inhaled glucocorticoid–formoterol combination as needed, and alternative options include the use of combination inhaled glucocorticoid–albuterol as needed or low-dose maintenance inhaled glucocorticoid plus a short-acting β_2-agonist reliever as needed.
- Combination inhaled glucocorticoid–formoterol maintenance and reliever therapy is the preferred treatment for moderate-to-severe asthma as compared with an inhaled glucocorticoid with long-acting β_2-agonist maintenance plus as-needed short-acting β_2-agonist reliever therapy.

fused with asthma are chronic obstructive pulmonary disease, heart failure, pulmonary embolism, and sarcoidosis.[7,8]

A personal history of atopy (e.g., atopic dermatitis or allergic rhinitis) or a strong family history of asthma is suggestive of asthma. Although asthma often presents in childhood, many children have a remission of symptoms in puberty and a recurrence in adulthood.[11] Approximately half of adults who present with what appears to be newly diagnosed asthma instead have had a recurrence of childhood asthma.[12,13]

Typical asthma triggers include exercise, cold air, and inhalant indoor and outdoor allergens.[7] Persons with asthma typically present with variable symptoms that may last from hours to days and resolve without intervention with avoidance of the trigger. Up to 10 to 25% of new-onset adult asthma cases are attributable to work-related exposures (e.g., wood dust, grain dust, and animal dander),[14,15] a correlation that emphasizes the importance of an occupational-history assessment and the identification of contact with known sensitizing agents to determine whether there is a temporal relationship between work exposures and symptoms.[16]

Approximately 7% of adults with asthma also have aspirin-exacerbated respiratory disease, which is characterized by cough, chest tightness, or wheeze within 30 to 120 minutes after ingestion of aspirin or any cyclooxygenase-1 inhibitor.[17] Obesity, anxiety, depression, and obstructive sleep apnea may also contribute to worsening asthma.

STRATEGIES AND EVIDENCE

GOALS OF ASTHMA THERAPY

The three main goals of asthma management are control of asthma symptoms, reduction in the risk of asthma exacerbations, and minimization of adverse effects of medications (e.g., side effects of oral glucocorticoid therapy).[7-10] Goals for asthma control are reduction in intensity and frequency of daytime and nighttime cough, chest tightness, wheezing, and shortness of breath; maintenance of normal daily activities without limitation caused by asthma symptoms, including symptoms related to school, work, and exercise; and lung function that is normal or nearly normal. Reduction of asthma risk focuses on prevention of severe exacerbations, which can be defined as deterioration that leads to treatment with oral glucocorticoids for 3 days or longer, an emergency department visit, or hospitalization.[7,8]

Treatment is focused on patient education, asthma trigger control, monitoring of symptoms and lung function, and pharmacologic therapy.[7-10] Empowerment of patients to be active participants in their asthma care is important. Such efforts include educating patients about strategies to identify and mitigate triggers, providing medications to be used for quick relief and those to be used for maintenance of control, encouraging adherence to daily controller therapy to reduce symptoms and minimize risk, and teaching the correct inhaler technique for each prescribed inhaler.[18] Some studies show that such patient education reduces the incidence of asthma exacerbations.[19-22]

A personalized, written asthma action plan is a tool that patients can use to assist in managing asthma at home. For patients whose symptoms occur after exposure to specific indoor allergens (confirmed by history and positive results on specific IgE blood or skin tests), multicomponent allergen-specific mitigation measures are recommended.[9] Symptom monitoring can be supported by the use of brief, patient-administered, validated instruments to assess asthma control, such as the five-item Asthma Control Test (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[23-25]

ASTHMA SEVERITY AND CONTROL

Asthma severity and control are categorized on the basis of consideration of daytime and nighttime symptoms that have occurred in the 4 weeks before presentation, the number of exacerbations leading to oral glucocorticoid use in the past year, and lung function.[7,8] Guidelines recommend a step up in therapy for patients with uncontrolled asthma and a step down in therapy after a patient's asthma has been controlled for 3 months with a stable treatment regimen.[7,8]

GUIDELINES FOR ASTHMA THERAPY

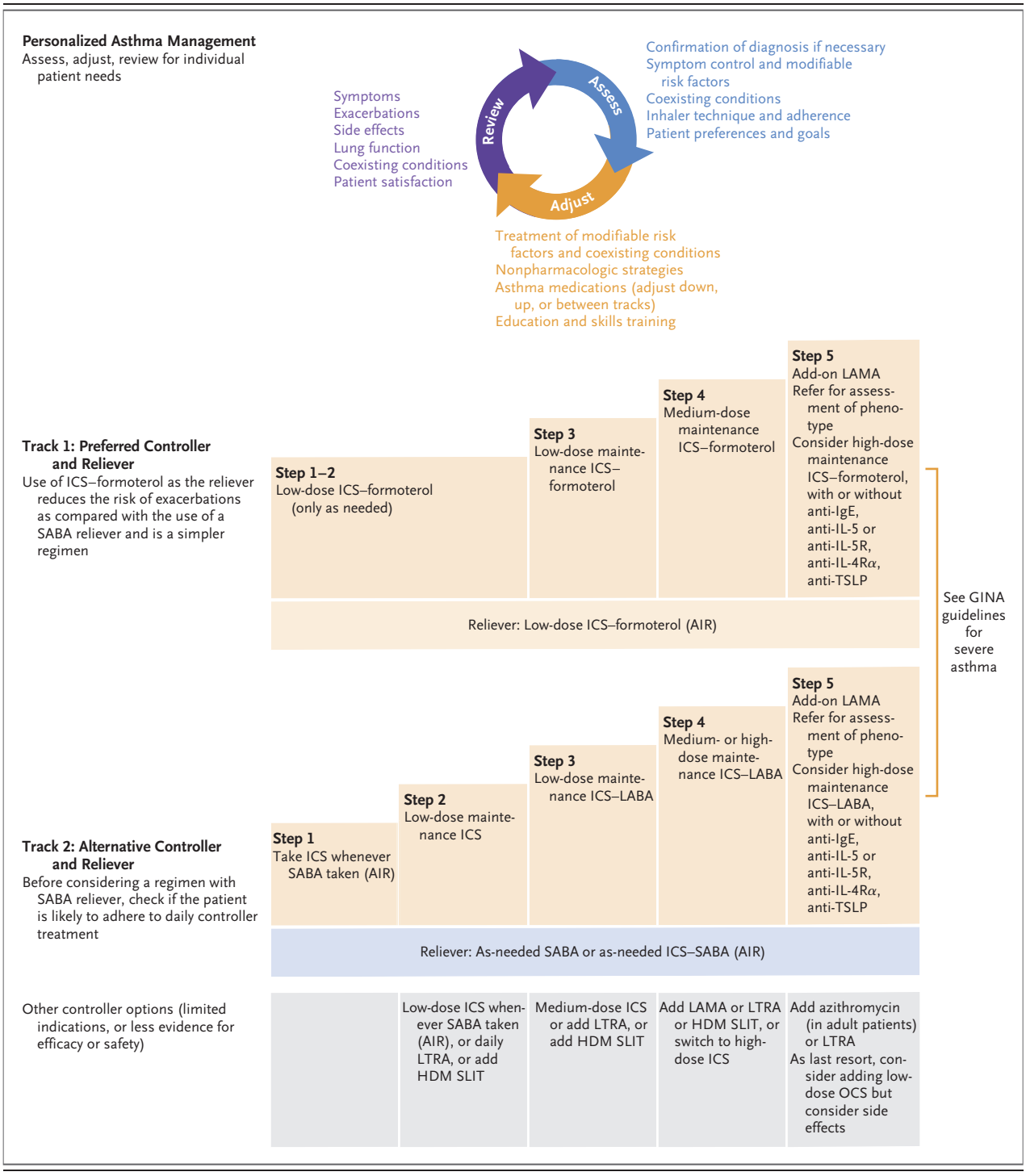
Figure 1 shows the most recent algorithm for asthma management in persons 12 years of age or older, according to the Global Initiative for Asthma (GINA) Science Committee, across categories of mild, moderate, and severe asthma.[8]

RELIEVER THERAPIES

In patients with occasional asthma symptoms, as-needed treatment with a combination of an inhaled glucocorticoid and a β_2-agonist is the current treatment of choice; the precise combination of inhaled glucocorticoid and β_2-agonist that is appropriate depends on availability and affordability. In a multinational, randomized, event-driven trial involving patients with moderate-to-severe asthma who were receiving inhaled glucocorticoid–containing maintenance therapy, the use of combination albuterol–budesonide therapy administered as needed at doses of 180 μg of albuterol and 160 μg of budesonide (two inhalations of 90 μg of albuterol and 80 μg of budesonide) reduced the occurrence of severe exacerbations by 27% as compared with as-needed albuterol alone.[26] In a pragmatic, open-label, randomized trial involving Black and Latinx adults with moderate-to-severe asthma, participants who were assigned to receive a dose of inhaled glucocorticoid whenever they used their SABA inhaler had 15% fewer severe exacerbations than participants who used the SABA inhaler alone.[27]

Data comparing combinations of an inhaled glucocorticoid and a long-acting β_2-agonist (LABA) or SABA as reliever therapies are limited. Formoterol is unique in that it is a fast-acting LABA and therefore works as a reliever medication, and its combination with an inhaled glucocorticoid has proven efficacy when used as a reliever therapy. However, data from direct comparisons between an inhaled glucocorticoid–formoterol combination reliever and an inhaled glucocorticoid–SABA combination reliever are lacking. In a study involving patients who were assigned to receive maintenance therapy with budesonide–formoterol, there were fewer occurrences of severe asthma exacerbations among patients assigned to receive budesonide–formoterol as the reliever than among those assigned to receive the SABA terbutaline alone as reliever therapy (relative risk, 0.78; confidence interval [CI], 0.67 to 0.91).[28] Inhaled glucocorticoid–formoterol combination therapy has received regulatory approval for use as a reliever therapy in the United Kingdom but not in the European Union or the United States. Overall, the regulatory approvals for combination inhalers as maintenance and reliever therapy are confusing and vary greatly among countries.[29,30]

Budesonide–formoterol and beclomethasone–formoterol are the only two inhaled glucocorticoid–formoterol formulations for which there is clinical evidence supporting their use as relievers in treating all levels of asthma severity.[31,32] Owing to safety concerns with the use of two different classes of LABAs, the use of inhaled glucocorticoid–formoterol combination reliever therapy is not recommended for use concurrently with inhaled glucocorticoid–LABA combination control therapy other than inhaled glucocorticoid–formoterol. Therefore, GINA describes different treatment tracks that are based on the type of LABA used (i.e., fast-onset formoterol or standard-onset LABA). GINA also recommends the use of inhaled glucocorticoid–formoterol as prophylaxis before exercise, given evidence that inhaled glucocorticoid–formoterol



is more protective than SABA against exercise-induced asthma.[8,32]

STEPS ONE AND TWO: THERAPY FOR MILD ASTHMA

At step one, the preferred treatment (GINA track one) for mild asthma is low-dose combination inhaled glucocorticoid–formoterol as needed for symptom relief; controller treatment is no longer recommended as part of step one (Table 1). Alternative treatments (track two) include the use of an inhaled glucocorticoid whenever SABA is taken (step one) and daily low-dose inhaled gluco-

Figure 1 (facing page). Global Initiative for Asthma 2023 (GINA) Personalized Asthma Management for Adolescents and Adults.

The cycle of assessment, adjustment, and review is recommended for each patient visit. First, confirm the diagnosis of asthma (if applicable) and assess symptom control, modifiable risk factors, coexisting conditions, adherence to and technique for inhaler use, and patient preferences and goals. Second, treat modifiable risk factors and coexisting conditions, use nonpharmacologic therapeutic strategies, adjust medications (up, down, and between tracks), and provide education and skills training. Third, review symptoms that occur during the day and at night, exacerbations, treatment side effects, lung function, coexisting conditions, and patient satisfaction. Treatment steps are grouped into tracks: track 1 (preferred) and track 2 (alternative) pharmacologic therapy for asthma that is mild (steps 1 and 2), moderate (steps 3 and 4), or severe (step 5). Orange shading denotes preferred treatment, and blue and gray denote alternative or nonpreferred treatment. AIR denotes antiinflammatory reliever, anti-IL5R anti–interleukin-5 receptor (monoclonal antibody), anti-IgE anti-immunoglobulin E (monoclonal antibody), anti-IL4Rα anti–interleukin-4 receptor alpha (monoclonal antibody), anti-IL5 anti–interleukin 5 (monoclonal antibody), anti-TSLP antithymic stromal lymphopoietin (monoclonal antibody), HDM SLIT house dust mite sublingual immunotherapy, ICS inhaled corticosteroid (i.e., glucocorticoid), LABA long-acting β_2-agonist, LAMA long-acting muscarinic antagonist, LTRA leukotriene receptor antagonist, OCS oral corticosteroid (i.e., glucocorticoid), and SABA short-acting β_2-agonist.

corticoid plus either as-needed SABA or as-needed inhaled glucocorticoid–SABA (step two). The evidence clearly shows a benefit of adding an inhaled glucocorticoid to a β_2-agonist for as-needed symptom relief, although comparative data are limited regarding which combinations are best.

Supporting this strategy are two Cochrane meta-analyses of as-needed inhaled glucocorticoid–formoterol combinations as compared with as-needed SABA, along with as-needed inhaled glucocorticoid–formoterol combinations as compared with a daily inhaled glucocorticoid plus SABA.[33,34] Two randomized, controlled trials involving 2997 participants showed with low-certainty evidence that, as compared with as-needed SABA, as-needed inhaled glucocorticoid–formoterol significantly reduced the odds of asthma exacerbations that led to the use of systemic glucocorticoids (odds ratio, 0.45; 95% CI, 0.34 to 0.60) and the odds of an asthma-related hospitalization or visit to an emergency department or urgent care center (odds ratio, 0.35; 95% CI, 0.20 to 0.60).[33] Four randomized, controlled trials involving 8065 participants showed with low-certainty evidence that, as compared with inhaled glucocorticoid for regular maintenance plus as-needed SABA, as-needed inhaled glucocorticoid–formoterol was not associated with lower odds of asthma exacerbations leading to treatment with systemic glucocorticoids (odds ratio, 0.79; 95% CI, 0.59 to 1.07) but did decrease the odds of an asthma-related hospitalization or visit to an emergency department or urgent care center (odds ratio, 0.63; 95% CI, 0.44 to 0.91).[34]

A separate network meta-analysis that included adult patients with mild asthma showed that the use of as-needed inhaled glucocorticoid–formoterol alone was associated with less risk of severe asthma exacerbations than either maintenance inhaled glucocorticoid plus as-needed SABA or as-needed SABA alone.[35] A pooled, post hoc analysis of the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 trials showed that patients who received as-needed budesonide–formoterol had 26% fewer severe exacerbations than patients who received daily budesonide. In contrast, there was no difference in the occurrence of severe asthma exacerbation with as-needed inhaled glucocorticoid–formoterol as compared with daily inhaled glucocorticoids among patients whose asthma was well controlled with the use of a low-dose daily inhaled glucocorticoid or leukotriene receptor antagonist plus as-needed SABA.[36]

Patient behaviors and preferences, as well as treatment access and cost, should also be considered in the shared decision-making process of treatment selection. Clinical trials that involved the use of electronic medication monitors to track real-time inhaler actuation have shown that patient-reported inhaled glucocorticoid use was greater than the objectively measured use and that patients' use of inhaled glucocorticoids decreased over time.[36,37] In a survey of a subgroup of participants in a randomized, controlled trial that assessed the addition of as-needed budesonide–formoterol to daily budesonide plus as-needed SABA, as-needed budesonide–formoterol was preferred by 90% of the participants who received it, and daily budesonide plus as-needed SABA was preferred by 40% of the participants who received that combination.[38] Some asthma

Table 1. Medications and Doses for GINA Track 1: Antiinflammatory Reliever–based Therapy.*

Treatment Step and Age	Medication and Strength	Doses Administered with DPI†
1 and 2 (antiinflammatory reliever only)		
6 to 11 yr	No evidence to date	1 inhalation as needed
12 to 17 yr	Budesonide 200 μg (delivered dose, 160 μg) and formoterol 6 μg (delivered dose, 4.5 μg)	1 inhalation as needed
≥18 yr	Budesonide 200 μg (delivered dose, 160 μg) and formoterol 6 μg (delivered dose, 4.5 μg)	1 inhalation as needed
3 (maintenance-and-reliever therapy)		
6 to 11 yr	Budesonide 100.0 μg (delivered dose, 80.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	1 inhalation once daily, plus 1 inhalation as needed
12 to 17 yr	Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	1 inhalation once or twice daily, plus 1 inhalation as needed
≥18 yr	One of the following regimens: Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg) Beclomethasone 100.0 μg (delivered dose, 84.6 μg) and formoterol 6.0 μg (delivered dose, 5.0 μg)	1 inhalation once or twice daily, plus 1 inhalation as needed
4 (maintenance-and-reliever therapy)		
6 to 11 yr	Budesonide 100.0 μg (delivered dose, 80.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	1 inhalation twice daily, plus 1 inhalation as needed
12 to 17 yr	Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	2 inhalations twice daily, plus 1 inhalation as needed
≥18 yr	One of the following regimens: Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg) Beclomethasone 100.0 μg (delivered dose, 84.6 μg) and formoterol 6.0 μg (delivered dose, 5.0 μg)	2 inhalations twice daily, plus 1 inhalation as needed
5 (maintenance-and-reliever therapy)		
6 to 11 yr	Not recommended	
12 to 17 yr	Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	2 inhalations twice daily, plus 1 inhalation as needed
≥18 yr	One of the following regimens: Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg) Beclomethasone 100.0 μg (delivered dose, 84.6 μg) and formoterol 6.0 μg (delivered dose, 5.0 μg)	2 inhalations twice daily, plus 1 inhalation as needed

* As recommended by the Global Initiative for Asthma 2023 (GINA) treatment track 1 (the preferred treatment track), the reliever is low-dose inhaled corticosteroid (i.e., glucocorticoid)–formoterol used as needed, with or without maintenance use of inhaled corticosteroid (i.e., glucocorticoid)–formoterol, depending on whether the patient has asthma that is mild (steps 1 and 2), moderate (steps 3 and 4), or severe (step 5). DPI denotes dry-powder inhaler and pMDI pressurized metered-dose inhaler.

† For delivery of antiinflammatory reliever only or maintenance-and-reliever therapy with budesonide–formoterol by means of a pMDI, patients should use an inhaler with half the strength of that used for the relevant DPI shown and should use double the number of doses shown. For example, at step 4 for a patient 12 years of age or older, budesonide–formoterol pMDI should be administered at a metered dose of 100 μg of budesonide and 3 μg of formoterol per inhalation in 4 inhalations twice daily plus 2 inhalations as needed.

experts have advocated changing the availability of inhaled glucocorticoid–formoterol from prescription to over-the-counter to increase patient access.[39]

STEPS THREE AND FOUR: THERAPY FOR MODERATE ASTHMA

Preferred step-three and -four treatment is single maintenance and reliever therapy (SMART) with

a low- or medium-dose inhaled glucocorticoid–formoterol combination (either budesonide–formoterol or beclomethasone–formoterol).[7,8] The SMART regimen may reduce cost and simplify treatment for patients, because only one inhaler is needed for both quick-relief and maintenance therapy. Alternative step-three and -four treatment includes either maintenance low- or medium-dose inhaled glucocorticoid–LABA plus as-needed SABA or as-needed combination inhaled glucocorticoid–SABA.[7,8] In a meta-analysis of randomized trials, switching patients with uncontrolled asthma at GINA step three to SMART at either step three or step four was associated with an increased time to the first severe asthma exacerbation, with a 29% reduction in risk as compared with stepping up to a step-four regimen of inhaled glucocorticoid–LABA maintenance plus a SABA reliever (hazard ratio, 0.71; 95% CI, 0.52 to 0.97). In addition, among patients at step three or step four with uncontrolled asthma, switching to SMART was associated with an increased time to the first severe asthma exacerbation and a 30% reduction in risk as compared to continuing therapy at the same treatment step (hazard ratio, 0.70; 95% CI, 0.58 to 0.85).[40]

STEP FIVE: THERAPY FOR SEVERE ASTHMA

Severe asthma is defined as a combination of symptoms and impairment in lung function that leads to treatment with a high-dose inhaled glucocorticoid plus a second controller medication (e.g., LABA) or nearly continuous oral glucocorticoid treatment.[41,42] Patients at step five (severe asthma) should be referred for expert evaluation (i.e., to an allergist–immunologist or pulmonologist), phenotyping, and add-on therapy. The severity of the asthma phenotype is determined on the basis of one or more of the following biomarkers: blood eosinophil level of at least 150 per microliter, fractional exhaled nitric oxide (FeNO) of at least 20 parts per billion, sputum eosinophils of at least 2%, sensitization to a perennial aeroallergen on skin-prick testing or blood tests for specific IgE, and a total IgE level of 30 to 700 IU per milliliter. Each patient's unique biomarker profile guides the selection of biologic therapy (e.g., sensitization to a perennial aeroallergen and elevated total IgE levels vs. elevated levels of blood eosinophils may lead to selection of omalizumab vs. other asthma biologic therapies, respectively). A long-acting muscarinic antagonist (LAMA) may be considered as add-on therapy for patients with asthma that is persistently uncontrolled despite treatment with a medium- or high-dose inhaled glucocorticoid–LABA. A meta-analysis showed that the addition of a LAMA to a medium- or high-dose inhaled glucocorticoid–LABA led to a 17% reduction in the risk of severe asthma exacerbation.[43]

Biologic therapies are an additional option, especially with regard to avoiding or minimizing exposure to treatment with high-dose inhaled glucocorticoids and oral glucocorticoids. The six biologic agents for use in the treatment of severe asthma are omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab, and the choice of biologic agent should include consideration of a variety of clinical and pragmatic factors, including biomarkers.[44] Although data from head-to-head clinical trials comparing biologics are lacking, each of these agents has shown efficacy as compared with placebo, with a 30 to 70% reduction in the relative risk of severe asthma exacerbations.[44-47]

AREAS OF UNCERTAINTY

Better strategies are needed for the objective evaluation of patient adherence and inhaler technique preceding a recommendation to step-up therapy. Clinical trials to evaluate the efficacy of digital inhalers and clinician dashboards (which provide the patient and health care professional with real-time data about medication-taking behavior and inhalation quality) regarding clinically important asthma outcomes are warranted. More studies to assess the role of biomarkers, such as blood and sputum eosinophil counts, FeNO levels, and serum total and allergen-specific IgE levels, are needed to better guide the selection of medications.[48,49]

GUIDELINES

The recommendations in this article are consistent with the guidelines of the National Asthma Education and Prevention Program Expert Panel-3 Report (and its 2020 focused update) as well as GINA (and its 2023 update).[7-9] GINA publishes an annual update to its guidelines, and the recommendations presented here are con-

cordant with the most recent GINA and National Asthma Education and Prevention Program reports and updates.

CONCLUSIONS AND RECOMMENDATIONS

With regard to the 47-year-old woman described in the vignette, her impairment (daytime symptoms) and risk (asthma exacerbations) warrant a step up in therapy. Because of the location of symptoms and timing of exacerbations, I suspect she has allergic asthma and concurrent allergic rhinitis due to pollens, and I would conduct skin testing for aeroallergens and provide education regarding relevant environmental-control measures and medical management. I would advise changing her treatment approach from GINA track 2 (alternative) to track 1 (preferred) therapy and increase treatment from step 2 to step 3 care, including a change to low-dose budesonide–formoterol as maintenance and reliever therapy. As compared with a SABA reliever alone, an inhaled glucocorticoid–formoterol reliever reduces severe exacerbations across treatment steps. The use of an inhaled glucocorticoid–formoterol combination for maintenance and reliever therapy simplifies the treatment regimen and allows for stepping up or stepping down without changing medication. I would also review inhaler technique, work with the patient to develop a written asthma action plan, and plan a follow-up visit in 3 months. (See inhaler technique video at https://www.nejm.org/doi/full/10.1056/NEJMra050380.)[50]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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