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Managing Asthma in Adolescents and Adults
2020 Asthma Guideline Update From the National Asthma Education and Prevention Program

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IMPORTANCE Asthma is a major public health problem worldwide and is associated with excess morbidity, mortality, and economic costs associated with lost productivity. The National Asthma Education and Prevention Program has released the 2020 Asthma Guideline Update with updated evidence-based recommendations for treatment of patients with asthma.

OBJECTIVE To report updated recommendations for 6 topics for clinical management of adolescents and adults with asthma: (1) intermittent inhaled corticosteroids (ICSs); (2) add-on long-acting muscarinic antagonists; (3) fractional exhaled nitric oxide; (4) indoor allergen mitigation; (5) immunotherapy; and (6) bronchial thermoplasty.

EVIDENCE REVIEW The National Heart, Lung, and Blood Advisory Council chose 6 topics to update the 2007 asthma guidelines based on results from a 2014 needs assessment. The Agency for Healthcare Research and Quality conducted systematic reviews of these 6 topics based on literature searches up to March-April 2017. Reviews were updated through October 2018 and used by an expert panel (n = 19) that included asthma content experts, primary care clinicians, dissemination and implementation experts, and health policy experts to develop 19 new recommendations using the GRADE method. The 17 recommendations for individuals aged 12 years or older are reported in this Special Communication.

FINDINGS From 20 572 identified references, 475 were included in the 6 systematic reviews to form the evidence basis for these recommendations. Compared with the 2007 guideline, there was no recommended change in step 1 (intermittent asthma) therapy (as-needed short-acting β_2-agonists [SABAs] for rescue therapy). In step 2 (mild persistent asthma), either daily low-dose ICS plus as-needed SABA therapy or as-needed concomitant ICS and SABA therapy are recommended. Formoterol in combination with an ICS in a single inhaler (single maintenance and reliever therapy) is recommended as the preferred therapy for moderate persistent asthma in step 3 (low-dose ICS-formoterol therapy) and step 4 (medium-dose ICS-formoterol therapy) for both daily and as-needed therapy. A short-term increase in the ICS dose alone for worsening of asthma symptoms is not recommended. Add-on long-acting muscarinic antagonists are recommended in individuals whose asthma is not controlled by ICS-formoterol therapy for step 5 (moderate-severe persistent asthma). Fractional exhaled nitric oxide testing is recommended to assist in diagnosis and monitoring of symptoms, but not alone to diagnose or monitor asthma. Allergen mitigation is recommended only in individuals with exposure and relevant sensitivity or symptoms. When used, allergen mitigation should be allergen specific and include multiple allergen-specific mitigation strategies. Subcutaneous immunotherapy is recommended as an adjunct to standard pharmacotherapy for individuals with symptoms and sensitization to specific allergens. Sublingual immunotherapy is not recommended specifically for asthma. Bronchial thermoplasty is not recommended as part of standard care; if used, it should be part of an ongoing research effort.

CONCLUSIONS AND RELEVANCE Asthma is a common disease with substantial human and economic costs globally. Although there is no cure or established means of prevention, effective treatment is available. Use of the recommendations in the 2020 Asthma Guideline Update should improve the health of individuals with asthma.

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Asthma is a major public health problem worldwide and is associated with excess morbidity, mortality, and economic costs associated with lost productivity.[1] Guidelines for asthma were first released in the United States in 1991 by the National Heart, Lung, and Blood Institute and were most recently updated in 2007.[2] An expert panel was convened in 2018 to update the asthma guidelines. In 2020, this expert panel published a selected topics update[3] to the 2007 National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) that was based on a formal needs assessment that had been conducted in 2014.[4] The 6 topics chosen for updating included intermittent inhaled corticosteroids (ICSs); add-on long-acting muscarinic antagonists (LAMAs); fractional exhaled nitric oxide (FeNO) measurement as a biomarker for asthma diagnosis, management and monitoring response to therapy; indoor allergen mitigation strategies; safety and efficacy of subcutaneous and sublingual immunotherapy; and bronchial thermoplasty. Eleven additional topics were identified[4] but not selected for the update because the National Heart, Lung, and Blood Advisory Council concluded there was insufficient new information at the time to support an update; asthma biologic therapy was considered an emerging therapeutic option at that time but was not selected as a priority topic.

This Special Communication describes the recommendations in the 2020 Asthma Guideline Update[3] for adolescents (ie, individuals aged 12-17 years) and adults (individuals aged 18 years or older) with asthma of all severities.

Methods

A detailed description of the methods used and the rationale for each recommendation is available in the 2020 Asthma Guideline Update.[3] Key questions for each priority topic were generated by the National Heart, Lung, and Blood Advisory Council (eTable in the Supplement). Evidence Practice Centers of the Agency for Healthcare Research and Quality were contracted to conduct systematic reviews for these key questions. Studies with children only, adults only, and mixed age populations were reviewed, and the combined evidence from these studies was used in making the recommendations. Some recommendations are age specific (eg, bronchial thermoplasty in adults), while other recommendations span the entire age range (eg, allergen mitigation). The protocols used and the results from the systematic reviews have been published.[5-9]

An expert panel (n = 19) composed of asthma content experts, primary care clinicians, and experts in dissemination and implementation and health care policy was convened in July 2018 and charged with using the completed systematic reviews to develop evidence-based recommendations for the 6 topics. Pharmacologic recommendations outside these 6 targeted areas were brought forward unchanged from the 2007 asthma guideline, even though new information might be available, because no systematic review had been conducted or the medication was not included in the key questions.

Members of the expert panel completed conflict of interest statements and were recused from participating in any discussion, writing, or voting on topics to which they had an apparent conflict according to the recommendations of the National Academy of Sciences[10] and consistent with the recommendations of the American College of Physicians.[11]

Box 1. Structure of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Platform

The strength of the recommendation is noted for each recommendation and is defined as follows:
- A strong recommendation for an intervention is a course of action that most individuals would want and should receive. Benefits outweigh risks, and clinicians should offer this intervention.
- A conditional recommendation for a course of action for clinicians is one that is appropriate for different individuals based on their values and preferences (often benefits and harms, but also including difficulty in implementing the course of action and cost, among other considerations) and uses shared decision-making. Most individuals in this situation will want the suggested course of action, but many will not.
- A conditional recommendation against an intervention is an intervention that most individuals will not want but a substantial number will want, and different choices by different individuals will be appropriate.
- A strong recommendation against an intervention is a course of action that most individuals should not receive but that some will want.

The certainty of evidence is noted for each recommendation and is defined as follows[3]:
- High certainty suggests that the true effect lies close to that of the effect estimate. In general, studies with high certainty of evidence include many participants and have low risk of bias, high precision, and consistent results.
- Moderate certainty suggests that the true effect is close to the effect estimate, but it could be substantially different. These studies have some problem, usually with either risk of bias, precision, or consistency.
- Low certainty suggests that the confidence in the effect estimate is low and the true effect may be substantially different from the effect estimate. These studies have usually 2 (or 1 very significant) problem(s) with risk of bias, precision, or consistency.

The expert panel updated the systematic reviews through October 2018 and used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) platform (**Box 1**)[12,13] to develop its recommendations. The Evidence Practice Centers used different databases relevant to their assigned topic to complete the systematic reviews, but all used EMBASE and most used PubMed.[5,6,8,9] Other databases that were used included the Cochrane Register of Controlled Trials,[5,7,8] the Cochrane Database of systematic reviews,[5,7] MEDLINE,[7] CINAHL,[6,9] and the gray literature.[5,6,9] Most systematic reviews were conducted for the period from inception of the database until March-April 2017 and were then updated by the expert panel to a standard end date of October 2018. Additional searches for other studies were not conducted.

Overall, 20 572 nonduplicated articles and other sources were reviewed, and a total of 475 relevant publications were included in the 6 systematic reviews. An additional 15 articles were included in the update by the expert panel. Results from these additional studies were considered in making the final recommendations but were not incorporated into the pooled estimates in the evidence to decision tables.

Critical outcomes that were used to assess the efficacy of the interventions were based on the 2012 Asthma Outcomes Workshop[14] and included asthma exacerbations (defined as either systemic corticosteroid use or asthma-specific emergency department visits or hospitalizations),[15] asthma control, and health-related quality of life. When available, validated instruments with minimally important differences were used. Other topic-specific critical or important outcomes included asthma symptoms, rescue medication use, and composite measures of exacerbations that combined systemic corticosteroids, asthma-specific emergency department visits, and asthma-specific hospitalizations.

Evidence profiles were created for each critical and important outcome, and effect estimates (with 95% confidence intervals) were determined across studies. For each outcome, the certainty of evidence was assessed from high to low, and studies were ranked lower on certainty based on risk of bias, imprecision (wide confidence intervals, boundaries that demonstrated both benefit and harm), inconsistency across studies, indirectness,[16] or publication bias.

Judgments based on the clinical significance or magnitude of the outcomes, overall certainty of evidence, net balance of harms and benefits, patient preferences, equity, acceptability, and feasibility of implementation (including initial and ongoing costs, amount of time and effort needed to implement the intervention, complexity of the intervention, and resource use) were used to develop the recommendations. Four types of recommendations were possible.[12,13] Recommendations could be "for" or "against" an intervention and could be "strong" or "conditional." A strong recommendation for an intervention is an intervention that most individuals would want and should be offered. A conditional recommendation for an intervention is an intervention that most individuals would want but many would not want, and different choices by different individuals will be appropriate. A conditional recommendation against an intervention is an intervention that most individuals would not want but a substantial number would want, and different choices by different individuals will be appropriate. Shared decision-making is an important component of treatment decisions for conditional recommendations. Patient characteristics and circumstances (eg, insurance, accessibility) as well as patient preferences should dictate whether an intervention with a conditional recommendation should be implemented. The new recommendations are listed in **Box 2**.

Pharmacologic Therapy for Managing Asthma in Individuals Aged 12 Years or Older

Two areas of asthma pharmacologic therapy, intermittent ICS treatment and use of add-on LAMAs, were evaluated, and a total of 7 recommendations in individuals aged 12 years or older were made (Box 2). Medications that are used at the same time but are available in the United States for use in asthma only in separate inhalers are presented with the word *plus*. For example, "ICS plus LAMA" indicates an ICS and a LAMA that are recommended for use as concomitant therapy but are currently only available in 2 separate inhalers. Medications that are administered at the same time but available and preferably used together in a single inhaler are presented as hyphenated. For example, "ICS-formoterol" refers to administration of these 2 medications in a single inhaler.

Updates to the Step Approach to Asthma Management

The EPR-3 recommended step pharmacologic therapy to achieve and maintain asthma control at the lowest effective therapeutic regimen.[2] Therapy is advanced 1 step until asthma control is achieved and reduced 1 step after asthma control has been maintained for a sufficient length of time, at least 3 consecutive months. The 2020 Asthma Guideline Update builds on the EPR-3 step therapy approach (**Figure**). The 2020 update did not revise or change the definitions of asthma severity proposed in the EPR-3, which used a combination of impairment (ie, symptom frequency, nocturnal awakenings, use of short-acting β_2-agonists (SABAs), interference with normal activity, and lung function) and risk of exacerbations requiring oral corticosteroids.[2]

As in the EPR-3, the revised step therapy recommendations list preferred therapies and alternative therapies (Figure). Preferred therapies indicate the best management options supported by the evidence. Alternative therapies represent management options that have been shown to be less effective than the preferred option(s) or have more limited evidence compared with the preferred option(s). However, alternative therapy options may still be appropriate in some patients. Some EPR-3 alternative therapies were more highly recommended than others, and this hierarchy has been maintained with first-order alternative therapies rated higher than second-order alternative therapies (**Table**). When the available evidence was insufficient or did not change a previous recommendation, the preferred and alternative therapies were left unchanged from the EPR-3 step diagram. New alternative therapies relative to EPR-3 alternative options are listed in order of preference or denoted as equivalent.

Step 1

Step 1 preferred therapy in the EPR-3 consisted of albuterol as needed for rescue therapy in individuals aged 12 years or older with intermittent asthma. This update does not change this recommendation. Recommendations for other potential therapies for step 1, such as using combination ICS-formoterol as needed for rescue therapy, were not made in this update because other potential therapies were not included in the key questions for the update (eTable in the Supplement).

Step 2

Step 2 preferred therapy in the EPR-3 was a daily low-dose ICS with a SABA as needed for rescue therapy for individuals with mild persistent asthma. The new preferred recommendation for step 2 therapy is either daily low-dose ICS therapy with an as-needed SABA for rescue therapy or an as-needed ICS plus a SABA used concomitantly (ie, one after the other) for rescue therapy (conditional recommendation, moderate certainty of evidence). If intermittent concomitant therapy is chosen, based on the intermittent therapy used in 3 of the 4 reviewed studies,[17-19] the recommended regimen would be 2 to 4 puffs of albuterol immediately followed by 80 to 250 µg of inhaled beclomethasone equivalent every 4 hours as needed for asthma symptoms. Another form of intermittent therapy for mild persistent asthma, as-needed ICS-formoterol for rescue therapy, was not addressed

Box 2. Expert Panel Recommendations for the 2020 Asthma Guideline Update[a]

Pharmacotherapy: Intermittent Inhaled Corticosteroids (ICSs)

- In individuals aged 12 years or older with mild persistent asthma, the expert panel conditionally recommends either a daily low-dose ICS and an as-needed short-acting β_2-agonist (SABA) for quick-relief therapy or an as-needed ICS and a SABA used concomitantly (conditional recommendation, moderate certainty of evidence).
- In individuals aged 4 years or older with mild to moderate persistent asthma who are likely to be adherent to daily ICS treatment, the expert panel conditionally recommends against a short-term increase in the ICS dose for increased symptoms or decreased peak flow (conditional recommendation, low certainty of evidence).
- In individuals aged 4 years or older with moderate to severe persistent asthma, the expert panel recommends ICS-formoterol therapy in a single inhaler used as both daily controller and reliever therapy (strong recommendation, high certainty of evidence for those older than 12 years) compared with either a higher-dose ICS as daily controller therapy and a SABA for quick-relief therapy or same-dose ICS–long-acting β_2-agonist (LABA) therapy as daily controller therapy and a SABA for quick-relief therapy.
- In individuals aged 12 years or older with moderate to severe persistent asthma, the expert panel conditionally recommends ICS-formoterol therapy in a single inhaler used as both daily controller and reliever therapy compared with higher-dose ICS-LABA therapy as daily controller therapy and a SABA for quick-relief therapy (conditional recommendation, high certainty of evidence).

Use of Long-Acting Muscarinic Antagonists (LAMAs) as Add-on Therapy

- In individuals aged 12 years or older with uncontrolled persistent asthma, the expert panel conditionally recommends against adding a LAMA to an ICS compared with adding a LABA to an ICS (conditional recommendation against, moderate certainty of evidence).
- If a LABA is not used, in individuals aged 12 years or older with uncontrolled persistent asthma, the expert panel conditionally recommends adding a LAMA to ICS controller therapy compared with continuing the same dose of ICS alone (conditional recommendation, moderate certainty of evidence).
- In individuals aged 12 years or older with uncontrolled persistent asthma, the expert panel conditionally recommends adding a LAMA to ICS-LABA therapy compared with continuing the same dose of ICS-LABA therapy (conditional recommendation, moderate certainty of evidence).

Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Diagnosis and Monitoring Treatment and Disease Activity

- In individuals aged 5 years or older for whom the diagnosis of asthma is uncertain using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed, the expert panel conditionally recommends addition of FeNO measurement as an adjunct to the evaluation process (conditional recommendation, moderate certainty of evidence).
- In individuals aged 5 years or older with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, the expert panel conditionally recommends addition of FeNO measurement as part of an ongoing asthma monitoring and management strategy that includes frequent assessments (conditional recommendation, low certainty of evidence).
- In individuals aged 5 years or older with asthma, the expert panel recommends against the use of FeNO measurement in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity. If used, it should be as part of an ongoing monitoring and management strategy (strong recommendation against, low certainty of evidence).

Allergen Reduction Strategies in Management of Asthma

- In individuals with asthma who do not have sensitization to specific indoor allergens or who do not have symptoms related to exposure to specific indoor allergens, the expert panel conditionally recommends against allergen mitigation interventions as part of routine asthma management (conditional recommendation against, low certainty of evidence).
- In individuals with asthma who have symptoms related to exposure to identified indoor allergens, confirmed by history taking or allergy testing, the expert panel conditionally recommends a multicomponent allergen-specific mitigation intervention (conditional recommendation, low certainty of evidence).
- In individuals with asthma who have sensitization or symptoms related to exposure to pests (cockroaches and rodents), the expert panel conditionally recommends the use of integrated pest management alone or as part of a multicomponent allergen-specific mitigation intervention (conditional recommendation, low certainty of evidence).
- In individuals with asthma who have sensitization or symptoms related to exposure to dust mites, the expert panel conditionally recommends impermeable pillow/mattress covers only as part of a multicomponent allergen mitigation intervention, not as a single-component intervention (conditional recommendation, moderate certainty of evidence).

Role of Subcutaneous and Sublingual Immunotherapy in Treatment of Allergic Asthma

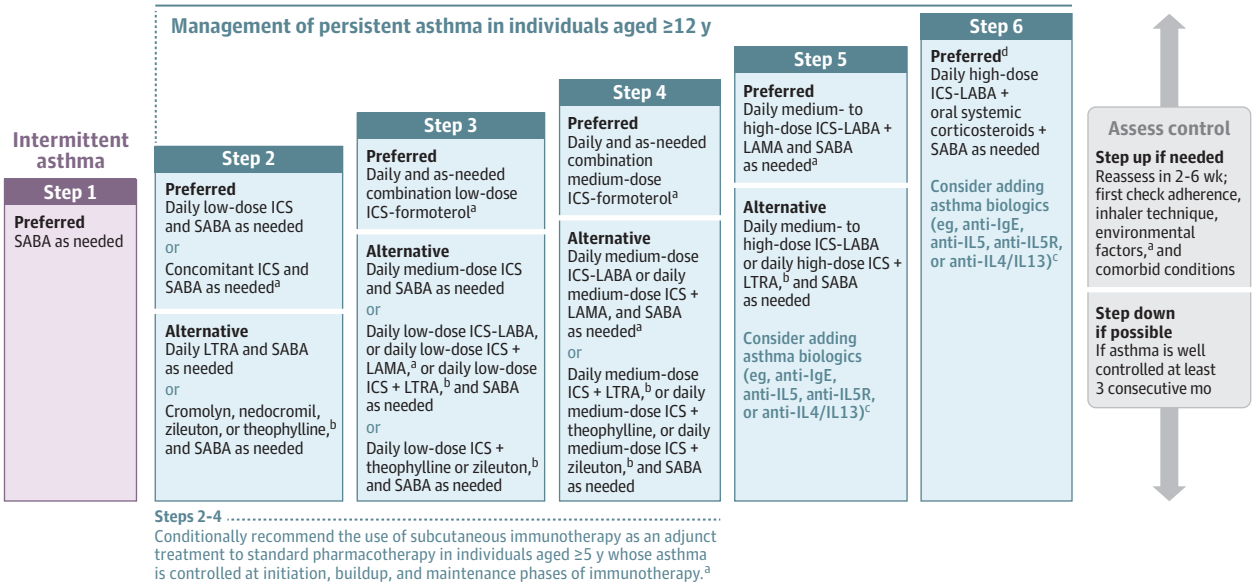
- In individuals aged 5 years or older with mild to moderate allergic asthma, the expert panel conditionally recommends the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals whose asthma is controlled at the initiation, buildup, and maintenance phases of immunotherapy (conditional recommendation, moderate certainty of evidence).
- In individuals with persistent allergic asthma, the expert panel conditionally recommends against the use of sublingual immunotherapy in asthma treatment (conditional recommendation, moderate certainty of evidence).

Bronchial Thermoplasty

- In individuals aged 18 years or older with persistent asthma, the expert panel conditionally recommends against bronchial thermoplasty (conditional recommendation, low certainty of evidence).
- Individuals aged 18 years or older with persistent asthma who place a low value on harms (short-term worsening symptoms and unknown long-term adverse effects) and a high value on potential benefits (improvement in quality of life, a small reduction in exacerbations) might consider bronchial thermoplasty.

[a] The expert panel made 19 recommendations, 2 of which involved only children aged 0 to 4 years. The following recommendations are not included in the list: (1) In children aged 0 to 4 years with recurrent wheezing, the expert panel recommends against FeNO measurement to predict future development of asthma (strong recommendation, low certainty of evidence). (2) In children aged 0 to 4 years with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections, the expert panel conditionally recommends starting a short course of daily ICSs at the onset of a respiratory tract infection with an as-needed SABA for quick-relief therapy compared with only an as-needed SABA for quick-relief therapy (conditional recommendation, high certainty of evidence).

Figure. Stepwise Approach for Management of Asthma in Individuals Aged 12 Years or Older



Each step: Assess environmental factors, provide patient education, and manage comorbidities.[a]

- In individuals with sensitization or symptoms related to **exposure to pests**, conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.[a,e]
- In individuals with sensitization or symptoms related to **exposure to identified indoor allergies**, conditionally recommend a multicomponent allergen-specific mitigation strategy.[a]
- In individuals with sensitization or symptoms related to **exposure to dust mites**, conditionally recommend impermeable pillow and mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single-component intervention.[a]
- Consult with asthma specialist if step 4 or higher is required. Consider consultation at step 3.

Quick-relief medication for all patients

- Use SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed.
- In steps 3 and 4, the preferred option includes the use of ICS-formoterol 1-2 puffs as needed up to a maximum total daily maintenance and rescue dose of 12 puffs (54 µg).[a]
- Increasing use of SABA >2 d/wk for symptom relief (not prevention of exercise-induced bronchoconstriction) generally indicates inadequate control and the need to step up treatment.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measure, self-reported control, and health care utilization are complementary and should be used on an ongoing basis, depending on the individual's clinical situation.

- The terms ICS-LABA and ICS-formoterol indicate combination therapy with both an ICS and a LABA, usually and preferably in a single inhaler.
- Where formoterol is specified in the steps, it is because the evidence is based on studies specific to formoterol.
- In individuals aged ≥12 y with persistent allergic asthma in which there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, fractional exhaled nitric oxide measurement is conditionally recommended as part of an ongoing asthma monitoring and management strategy that includes frequent assessment.
- Bronchial thermoplasty was evaluated in step 6. The outcome was a conditional recommendation against the therapy.

Figure adapted from the 2020 Asthma Guideline Update.[3] AHRQ indicates Agency for Healthcare Research and Quality; ICS, inhaled corticosteroid; Ig, immunoglobulin; IL, interleukin; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist (inhaled).

[a] New recommendation based on the 2020 Asthma Guideline Update.

[b] Cromolyn, nedocromil, LRTAs (including zileuton and montelukast), and theophylline were not considered for the update. These have limited availability for use in the US and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The US Food and Drug Administration issued a boxed warning for montelukast in March 2020 because of adverse effects related to serious behavior- and mood-related changes.

[c] The AHRQ systematic reviews that informed the update did not include studies that examined the role of asthma biologics (anti-IgE, anti–IL-5, anti–IL-5R, and anti–IL-4/IL-13). Thus, this report does not contain specific recommendations for use of biologics in asthma in steps 5 and 6.

[d] Data on the use of LAMA therapy in individuals with severe persistent asthma (step 6) were not included in the AHRQ systematic review[7]; thus, no recommendations were made.

[e] Pests refers to mice and cockroaches, which were specifically examined in the AHRQ systematic review.[6]

in this update because this therapy was not included in the key questions formulated for the update.

Step 3

Two changes were made in the EPR-3 step 3 recommendations for moderate persistent asthma. The first was the recommendation for single maintenance and reliever therapy (SMART) with low-dose ICS-formoterol therapy as the preferred daily controller and as-needed rescue therapy option (strong recommendation, high certainty of evidence). SMART therapy is described in detail in its own section later in the article. The second change is the addition of a daily low-dose ICS plus a LAMA (see "Use of LAMAs as Add-on Therapy" later in the article) with an as-needed SABA for rescue therapy as an additional alternative therapeutic option for step 3 therapy. If a long-acting

Table. Recommendations for Pharmacologic Step Therapy for Managing Asthma in Adolescents (Aged 12-17 Years) and Adults (Aged 18 Years or Older)[3a]

Asthma severity	Step	Preferred therapy	Alternative therapies[b] First order	Alternative therapies[b] Second order
Intermittent	1	As-needed SABA	None	None
Persistent				
Mild	2	Daily low-dose ICS and as-needed SABA or As-needed concomitant ICS and SABA (conditional recommendation, moderate certainty of evidence)[c]	Daily LTRA and as-needed SABA[d] or Cromolyn, nedocromil, or theophylline and as-needed SABA[d]	None
Moderate	3	Daily and as-needed combination low-dose ICS-formoterol (SMART) (strong recommendation, high certainty of evidence)[c,e]	Daily medium-dose ICS and as-needed SABA or Daily low-dose ICS-LABA and as-needed SABA	Daily low-dose ICS plus LAMA and as-needed SABA (conditional recommendation, moderate certainty of evidence)[c,f] or Low-dose ICS plus LTRA and as-needed SABA[d] or Daily low-dose ICS plus theophylline or Zileuton and as-needed SABA[d]
	4	Daily and as-needed combination medium-dose ICS-formoterol (SMART) (strong recommendation, high certainty of evidence)[c,e]	Daily medium-dose ICS-LABA and as-needed SABA	Daily medium-dose ICS plus LAMA and as-needed SABA (conditional recommendation, moderate certainty of evidence)[c] or Daily medium-dose ICS plus LTRA or Theophylline or Zileuton and as-needed SABA[d]
Severe	5[g]	Daily medium- to high-dose ICS-LABA plus LAMA and as-needed SABA (conditional recommendation, moderate certainty of evidence)[c]	Daily high-dose ICS-LABA and as-needed SABA	High-dose ICS plus LTRA and as-needed SABA[d]
	6[g]	Daily high-dose ICS-LABA plus oral systemic corticosteroids and as-needed SABA	None	None

Abbreviations: EPR-3, Expert Panel Report 3; FDA, US Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist (inhaled); SMART, single maintenance and reliever therapy.

[a] New recommendations for pharmacologic therapies are footnoted individually with a "c." Nonfootnoted recommendations are pulled through from the EPR-3. Originally recommended in the EPR-3, a stepwise approach to pharmacologic management of asthma is again recommended in the 2020 Asthma Guideline Update. The type, amount, and scheduling of medication are directly related to asthma severity for initiating therapy and to level of asthma control for adjusting therapy. The 2020 update did not revise or change the definitions of asthma severity proposed in the EPR-3, which used a combination of impairment (ie, symptom frequency, nocturnal awakenings, use of short-acting β_2-agonists, interference with normal activity, and lung function) and risk of exacerbations requiring oral corticosteroids.[2]

[b] Alternative therapies are listed according to their recommended priority from the EPR-3. First-order alternative therapies are recommended more highly than second-order therapies. Within the first-order and second-order alternative therapy lists, there is no prioritization. First-order alternative therapies were pulled through from the EPR-3 in step 2 and were preferred therapies in the EPR-3 for steps 3 through 5.

[c] New recommendation.

[d] Cromolyn, nedocromil, LTRAs (including zileuton and montelukast), and theophylline were not considered for this update. These have limited availability for use in the US and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a boxed warning for montelukast in March 2020 because of adverse effects related to serious behavior- and mood-related changes.

[e] Medications that are used at the same time but are available in the US for use in asthma only in separate inhalers are presented with the word *plus*. For example, "ICS plus LAMA" indicates an ICS and a LAMA that are recommended for use as concomitant therapy (ie, one after the other) but currently are available in the US only in 2 separate inhalers. Medications that are administered at the same time but available and preferably used together in a single inhaler are presented as hyphenated. Thus, "ICS-formoterol" and "ICS-LABA" indicate administration of these 2 medications in a single inhaler.

[f] LAMAs include aclidinium, glycopyrrolate, tiotropium, and umeclidinium. As of October 2020, the tiotropium inhaler (Spiriva Respimat; Boehringer Ingelheim) and umeclidinium (used in a combination inhaler with fluticasone furoate and vilanterol) are FDA approved for treatment of asthma.

[g] Asthma biologics could be considered in steps 5 and 6 but were not addressed in the 2020 Asthma Guideline Update.

β_2-agonist (LABA) is not used, in individuals aged 12 years or older with uncontrolled persistent asthma, the expert panel conditionally recommends adding a LAMA to ICS controller therapy compared with continuing the same ICS dose alone (conditional recommendation, moderate certainty of evidence).

Step 4

Similar to step 3, 2 changes were made in the 2020 Asthma Guideline Update's step 4 recommendations for moderate-severe persistent asthma. SMART therapy with medium-dose ICS-formoterol is the preferred daily controller and as-needed rescue therapy option, and a daily medium-dose ICS plus a LAMA with an as-needed SABA for rescue therapy is an additional alternative therapeutic option. In individuals aged 4 years or older with moderate to severe persistent asthma, the expert panel recommends ICS-formoterol therapy in a single inhaler used as both daily controller and reliever therapy compared with either a higher-dose ICS as daily controller therapy and a SABA for quick-relief therapy or a same-dose ICS-LABA

as daily controller therapy and a SABA for quick relief therapy (strong recommendation, high certainty of evidence for individuals aged 12 years or older). If a LABA is not used, in individuals aged 12 years or older with uncontrolled persistent asthma, the expert panel conditionally recommends adding a LAMA to ICS controller therapy compared with continuing the same dose of ICS alone (conditional recommendation, moderate certainty of evidence).

Steps 5 and 6

The only change in steps 5 and 6 from the EPR-3 recommendations is the designation of a daily medium- to high-dose ICS-LABA plus a LAMA as the preferred step 5 controller with an as-needed SABA for rescue therapy for severe persistent asthma. In individuals aged 12 years or older with uncontrolled persistent asthma, the expert panel conditionally recommends adding a LAMA to ICS-LABA therapy compared with continuing the same ICS-LABA dose (conditional recommendation, moderate certainty of evidence).

The use of SMART in steps 5 and 6 was not addressed in this update because SMART therapy for steps 5 and 6 was not included in the key questions formulated for the update. Biologic therapy was not evaluated because it was considered an emerging topic at the time and not chosen for updating.

The expert panel continues to recommend assessing adherence, inhaler technique, environmental triggers, and comorbid conditions prior to stepping up care.

Rescue Use of ICSs

The EPR-3 recommended against a doubling of the ICS dose in response to increased symptoms in adolescents (aged 12-17 years) and adults (aged 18 years or older) with asthma who were being treated with daily ICSs. The new evidence reviewed in this update confirmed, extended, and clarified that recommendation. In individuals aged 4 years or older with mild to moderate persistent asthma who are likely to be adherent to daily ICS treatment, the expert panel conditionally recommends against a short-term increase in the ICS dose for increased symptoms or decreased peak flow (conditional recommendation, low certainty of evidence).

For individuals with mild to moderate persistent asthma who are likely to be adherent to daily ICS treatment, a short-term increase in the ICS dose alone for increased symptoms or decreased peak flow is not recommended (conditional recommendation against, low certainty of evidence). This recommendation addresses temporarily increasing the dose of ICS that is otherwise taken alone as controller therapy in response to a measure of worsening asthma. A short-term increase in ICS dose refers to a doubling, quadrupling, or quintupling of the regular daily dose.

In adolescents aged 12 years or older and adults, doubling, quadrupling, or quintupling of the regular daily dose of ICS did not significantly reduce exacerbations in 3 studies included in the systematic review.[20-22] A 2018 study[23] showed a modest but significant increase in time to a severe exacerbation (adjusted hazard ratio for time to first exacerbation, 0.81; 95% CI, 0.71-0.92; P = .002) and a decrease in the incidence rate of use of corticosteroids in individuals whose action plan included a quadrupling of the ICS. Differences between this study and the studies in the systematic review included lack of placebo, lack of blinding, and low baseline adherence. Specifically, in this study, only 50% of the 562 participants in the quadrupling group and 42% of the 552 participants in the nonquadrupling group were judged by the investigators as having good adherence. However, as noted by the expert panel, adherence in this study may be more similar to adherence in routine clinical practice, and adherence in the randomized clinical trials included in the systematic review would likely be higher than in most clinical settings. Thus, in the opinion of the expert panel, this recommendation not to temporarily increase the ICS dose for an increase in asthma symptoms would apply most specifically to individuals who are likely to be adherent to their daily ICS regimen. In contrast, an increase in ICSs in the action plan of individuals in whom adequate adherence is uncertain seems reasonable. How to assess adherence or the threshold for adequate adherence in relationship to this recommendation cannot be determined from the reviewed studies. Based on this study,[23] a short-term increase in ICS dose could be implemented in individuals older than 16 years as a quadrupling of ICS in response to an increased need for reliever therapy, more interference with sleep due to asthma, or a peak flow of less than 80% of the individual's normal level.

Box 3. Considerations Regarding Single Maintenance and Reliever Therapy (SMART)

- SMART is recommended in adolescents (aged 12-17 years) and adults (aged 18 years or older) with moderate persistent asthma as the preferred therapy for steps 3 and 4 (strong recommendation, high certainty of evidence).
- SMART has been reported only with formoterol as the long-acting β_2 agonist, which is why the recommendation is specific to formoterol therapy.
- Inhaled corticosteroid (ICS)–formoterol therapy should not be used as reliever therapy in adults using ICS-salmeterol maintenance therapy. The safety profile of this use is not known.
- Regular daily use in SMART is defined as 1 to 2 puffs once to twice daily.
- As-needed use in SMART is defined as 1 to 2 puffs (4.5 µg of formoterol per puff) every 4 hours as needed for asthma symptoms, up to a maximum of 12 total puffs per day for individuals aged 12 years or older.
- Adults with asthma who have experienced an asthma exacerbation in the prior year may be particularly good candidates for SMART.
- Individual circumstances, such as cost, formulary considerations, or medication intolerance, may mitigate against using SMART. SMART is not currently approved by the US Food and Drug Administration for use as recommended by these guidelines.
- The recommended alternative therapy of maintenance ICS–long-acting β_2-agonist therapy with a short-acting β_2-agonist as reliever therapy does not need to be changed if it is providing adequate control.

Single Maintenance and Reliever Therapy

The 2020 Asthma Guideline Update recommends SMART as the preferred daily controller therapy and as the preferred as-needed rescue therapy for step 3 (low-dose ICS-formoterol therapy) and step 4 (medium-dose ICS-formoterol therapy) (**Box 3**). This is a strong recommendation based on a high certainty of evidence from 10 studies involving a total of 20 817 children (aged 4-11 years), adolescents (aged 12-17 years), and adults (aged 18 years or older).[3] Multiple studies demonstrate that SMART is more effective in reducing a composite measure of exacerbations vs 3 different comparators

Box 4. Considerations Regarding Inhaled Long-Acting Muscarinic Antagonists (LAMAs)

- LAMAs can be be used for long-term asthma control in ambulatory settings but not to treat acute asthma in the emergency department or in inpatient settings.
- LAMAs should not be used in individuals with or at risk of urinary retention or glaucoma.
- In treatment of moderate persistent asthma (steps 3 and 4), inhaled corticosteroid–long-acting β_2-agonist (ICS-LABA) therapy is the preferred controller regimen for steps 3 and 4, while ICS-LAMA therapy is a secondary alternative (conditional recommendation, moderate certainty of evidence).
- Adding a LAMA to ICS-LABA therapy is recommended for step 5 (conditional recommendation, moderate certainty of evidence).
- Use of add-on LAMA therapy in step 6 was not addressed in this update.

(a higher daily dose of an ICS with an as-needed SABA, a daily same-dose ICS plus LABA and an as-needed SABA, and a higher daily-dose ICS plus LABA and an as-needed SABA).[24-31] One of these studies[24] included children only, but is the only study comparing a higher dose of ICSs alone with SABAs as needed for rescue therapy with SMART. The remaining studies included individuals aged 12 years or older.

Considerations regarding use of SMART are summarized in Box 3. SMART has only been used with formoterol as the LABA. Compared with other currently available LABAs, formoterol has a rapid onset of action and a dose range that allows use more than twice daily. SMART should not be combined with other LABAs because the safety profile of ICS-formoterol therapy used with other ICSs-LABAs is not known. Regular daily use recommended in studies of SMART is 1 to 2 puffs once to twice daily (depending on age, asthma severity, and dose of ICS in the ICS-formoterol preparation).[3] As-needed use is 1 to 2 puffs (4.5 µg of formoterol per puff) every 4 hours as needed for asthma symptoms, up to a maximum of 12 total puffs per day, for individuals aged 12 years or older.[3]

SMART is used with a single inhaler containing both formoterol and an ICS (primarily budesonide in the reviewed studies; beclomethasone in 1 study[26]). The comparative regimens used in the studies to address the efficacy and safety of SMART therapy required 2 inhalers: the controller (an ICS or an ICS-LABA) and the as-needed reliever or rescue therapy (SABA). The recommended first-order alternative therapy of a daily ICS-LABA with an as-needed SABA for rescue therapy (Table) does not need to be changed if it is providing adequate control, but individuals whose asthma is uncontrolled by such therapy should receive the preferred SMART if possible before increasing to a higher step of therapy.

Summary of Updated Intermittent ICS Recommendations

In individuals with mild persistent asthma, either a daily low-dose ICS with an as-needed SABA or an as-needed concomitant ICS plus a SABA is recommended (step 2). In individuals aged 12 years or older with mild persistent asthma, the expert panel conditionally recommends either a daily low-dose ICS and an as-needed SABA for quick-relief therapy or an as-needed ICS and SABA used concomitantly (conditional recommendation, moderate certainty of evidence).

In individuals with mild to moderate persistent asthma who are likely to be adherent to daily ICS treatment, a short-term increase in the ICS dose alone for increased symptoms or decreased peak flow is not recommended. In individuals with moderate to severe persistent asthma, ICS-formoterol therapy in a single inhaler used as both daily controller and as-needed rescue therapy is recommended as the preferred step 3 and step 4 pharmacologic therapy (Table). In individuals aged 4 years or older with moderate to severe persistent asthma, the expert panel recommends ICS-formoterol therapy in a single inhaler used as both daily controller and reliever therapy compared with either a higher-dose ICS as daily controller therapy and a SABA for quick-relief therapy or a same-dose ICS-LABA as daily controller therapy and a SABA for quick relief therapy (strong recommendation, high certainty of evidence for age 12 years or older).

Use of LAMAs as Add-on Therapy

For the first time, the 2020 Asthma Guideline Update included recommendations for the use of LAMAs for asthma (**Box 4**). The key questions that were addressed included use of LAMAs as an add-on treatment to a daily ICS compared with either a same-dose or higher-dose ICS or as an add-on treatment to a combination ICS-LABA (step 3, 4, or 5 therapy) (eTable in the Supplement).[7] LAMA therapy is recommended for use for long-term asthma control in the ambulatory setting and not to treat acute asthma in the emergency department or in the inpatient setting. LAMA therapy is not recommended for use in individuals with or at risk of urinary retention or glaucoma (Box 4). Three recommendations for adolescents and adults were made (Box 2).

First, the expert panel recommended against a daily ICS plus a LAMA with an as-needed SABA for rescue therapy compared with a daily ICS-LABA with an as-needed SABA for rescue in step 3 therapy because of a more favorable benefit-harm profile for add-on LABAs (conditional recommendation against, moderate certainty of evidence). In other words, in individuals with uncontrolled persistent asthma using a daily ICS with an as-needed SABA for rescue therapy, the addition of a LABA to daily ICS therapy is preferred over the addition of a LAMA to daily ICS therapy (step 3). Although there were no substantial differences in beneficial effects on critical outcomes between a daily ICS plus a LAMA with an as-needed SABA for rescue therapy and a daily ICS-LABA[32-36] with an as-needed SABA, there was concern about the potential for excess harm with ICS plus LAMA therapy compared with ICS-LABA therapy reported in one comparative effectiveness study involving Black adults.[37] In this study, there were 19 asthma-related hospitalizations in the ICS plus LAMA group (n = 532) compared with 10 in the ICS plus LABA group (n = 536) (P = .09). The adjusted rate ratio of asthma-related hospitalizations was 2.6-fold higher (95% CI, 1.14-5.91; P = .02) in the ICS plus LAMA group compared with the ICS plus LABA group, and 2 asthma-related deaths occurred in the ICS plus LAMA group compared with 0 in the ICS plus LABA group.

Second, in individuals with uncontrolled asthma using a daily ICS who are unable to use LABA therapy, add-on LAMA therapy (a daily ICS plus a LAMA with an as-needed SABA for rescue therapy; step 3 therapy) results in a small reduction in asthma exacerbations but no change in other critical outcomes compared with continuing the same dose of ICS therapy with an as-needed SABA for rescue therapy alone.[32-34,38-40] The expert panel concluded that the balance of evidence demonstrates a small benefit of the addition of a LAMA to ICS therapy vs continuing same-dose ICS therapy; however, because of a small concern related to harm as noted, the expert

panel preferentially recommends adding a LABA to ICS therapy, and adding a LAMA to ICS therapy only in those for whom LABAs cannot be used.

There was insufficient evidence to make a recommendation regarding a daily ICS plus an add-on LAMA (with an as-needed SABA for rescue therapy) compared with a daily ICS plus add-on montelukast or doubling the dose of the ICS with an as-needed SABA for rescue therapy.

Third, there was a conditional recommendation with moderate certainty of evidence for add-on LAMA therapy to ICS-LABA combination therapy with an as-needed SABA (step 5) in individuals whose asthma is uncontrolled on same-dose ICS-LABA therapy (step 4). The addition of a LAMA to combined ICS-LABA therapy was associated with an improvement in asthma control and in quality of life with no change in exacerbations.[38,41]

Summary of LAMA Recommendations

Add-on LAMA therapy is recommended for many individuals aged 12 years or older with uncontrolled asthma as a secondary alternative to SMART in both step 3 and step 4 therapy (the preferred alternative therapy is an ICS-LABA with an as-needed SABA in both step 3 and step 4) and as the preferred add-on therapy in step 5 in combination with an ICS-LABA (Table) and an as-needed SABA for rescue therapy. The use of add-on LAMA therapy in step 6 was not addressed in this update.

Utility of FeNO in Asthma Diagnosis and Monitoring Treatment and Disease Activity

The role of FeNO testing in asthma diagnosis and monitoring was not addressed in the EPR-3. The expert panel addressed the role of FeNO for diagnosing asthma and the clinical utility of FeNO in selecting medications, monitoring treatment, and monitoring disease activity in individuals aged 5 years or older. Three recommendations were made for adults (Box 2). Some of the recommendations were based on studies in children.

FeNO is used as a biomarker of type 2 inflammation. Type 2 inflammation, also known as eosinophilic inflammation in the airway, is characterized by airway immune responses mediated primarily by eosinophils, mast cells, basophils, type 2 helper T lymphocytes, group 2 innate lymphoid cells, and immunoglobulin E (IgE)–producing B cells.[42] FeNO testing involves minimal patient effort (exhaling into a monitoring device) and few adverse effects, and can be performed by most individuals aged 12 years or older. However, because specialized equipment and trained personnel are required, FeNO testing is typically available only in a subspecialty setting, which may limit access.

Box 5. Considerations for Fractional Exhaled Nitric Oxide (FeNO) Testing

- FeNO testing involves exhaling at a steady state through a device that measures the level of nitric oxide. The test is easily performed by most individuals and has no significant adverse effects. The cost of the equipment and the maintenance of supplies may not be cost-effective for many primary care offices. Referral to a specialist office for testing may be necessary.
- Measurement of fractional exhaled nitric oxide is recommended
  - When the diagnosis of asthma is uncertain despite history, clinical findings, and spirometry testing with bronchodilator (conditional recommendation, moderate certainty of evidence).
  - To monitor and manage asthma in the context of history, clinical findings, and spirometry. In monitoring and managing asthma, FeNO testing needs to be performed frequently (conditional recommendation, low certainty of evidence).
- FeNO is not recommended as a single test either for asthma diagnosis or to monitor and manage asthma (conditional recommendation, moderate certainty of evidence).
- FeNO test results in isolation are not recommended to predict the severity or risk of asthma exacerbations or to assess asthma control (strong recommendation, low certainty of evidence).
- FeNO levels are increased and decreased by numerous factors:
  - FeNO levels less than 25 ppb are found in individuals who are taking corticosteroids for any reason, including asthma. Low levels are also found in individuals with non–type 2 asthma, in individuals with obesity, and in those who smoke. Individuals with nonasthma diagnoses such as cystic fibrosis, vocal cord dysfunction, chronic obstructive pulmonary disease, and ciliary dyskinesia also demonstrate low levels of FeNO.
  - Intermediate levels (25-50 ppb) are especially difficult to interpret but can be present in individuals with asthma who are partially adherent to corticosteroid therapy or whose asthma is inadequately controlled by their current corticosteroid therapy.
  - FeNO levels greater than 50 ppb are found in individuals with type 2 asthma or eosinophilic bronchitis and in individuals without asthma but with allergic sensitization. Individuals with levels greater than 50 ppb are likely to respond to corticosteroids.
- FeNO may be considered as additional information to evaluate uncontrolled asthma, inhaled corticosteroid adherence, and stability for a step down in therapy. Elevated FeNO levels in this circumstance could suggest persistent type 2 inflammation and/or poor adherence to inhaled corticosteroids, and would mitigate against step-down therapy, while normal FeNO levels could suggest absence of persistent type 2 inflammation and adherence to inhaled corticosteroids, and support step-down therapy.
- Using FeNO test results as an isolated test to predict the severity of an asthma exacerbation or risk of future asthma exacerbations is not recommended (strong recommendation, low certainty of evidence).

Use of FeNO in Asthma Diagnosis

The expert panel recommends FeNO measurement as an adjunct test to diagnose asthma (conditional recommendation, moderate certainty of evidence). There is no single definitive test for diagnosing asthma; a diagnosis of asthma requires integrating information on symptoms and clinical course, as well as testing. Initial testing for asthma should include spirometry with bronchodilator administration. When the diagnosis is still uncertain—based on history, physical examination, and spirometry, or if an individual cannot perform spirometry—FeNO can be a useful adjunct test. FeNO results alone are not diagnostic; results need to be interpreted in conjunction with all the other available clinical and diagnostic information.

Clinicians should be aware that some individuals with asthma have low levels of FeNO and some individuals without asthma have high levels of FeNO (**Box 5**).[43] For example, individuals with noneosinophilic asthma have low levels of FeNO, and factors such as smoking and obesity are associated with lower levels of FeNO. Individuals with asthma who use corticosteroids have reduced levels of FeNO.

Box 6. Considerations for Allergen Mitigation in Adults With Asthma

- All individuals with asthma of all severities should undergo an environmental assessment for exposure to allergens at home and at work, which should include either a history of symptoms on exposure or evidence of sensitization either by allergy skin testing or allergen-specific immunoglobulin E (Expert Panel Report 3).
- Mitigation interventions are not recommended in individuals with no history of exposure and in whom there is no evidence of either sensitization or symptoms with exposure (conditional recommendation, low certainty of evidence).
- Single-component allergen-specific interventions are not recommended (with the exception of integrated pest management) (conditional recommendation, low certainty of evidence). This includes use of acaricides, dust mite–impermeable pillow and mattress covers, carpet removal, and high-energy particulate air (HEPA) purifiers/air filtration.
- When used, multicomponent allergen-specific intervention strategies are recommended (conditional recommendation, low certainty of evidence). Examples of multicomponent mitigation strategies include:
  - For rodents and/or cockroaches, integrated pest management including measures to block infestation (eg, filling holes in walls, reducing standing water) and abatement (eg, traps, fumigation) (there is a public health component to this recommendation)
  - For dust mites, combinations of dust mite–impermeable pillow and mattress covers, HEPA filter–equipped vacuum cleaner, carpet and curtain removal, and cleaning products
  - For mold, HEPA purifiers and mold abatement

Conversely, some nonasthma conditions are associated with high levels of FeNO, including allergic rhinitis and eosinophilic bronchitis. FeNO levels need to be interpreted within the full clinical context, considering the complete history and comorbid conditions, when used as an adjunct test to diagnose asthma.

More than 50 studies that investigated the role of FeNO in diagnosing asthma were reviewed[3]; there were no randomized clinical trials of FeNO for the diagnosis of asthma. The studies included different populations, so this recommendation is applicable to a broad population. In addition, the studies used varying protocols with different FeNO thresholds, so the certainty of evidence for this recommendation was reduced.

FeNO in Asthma Management

Fractional exhaled nitric oxide testing is recommended as part of an ongoing asthma monitoring and management strategy to choose and/or adjust anti-inflammatory therapy (conditional recommendation, low certainty of evidence) when used alongside all other clinical information. Other clinical information should include history, clinical findings, and spirometry. This recommendation is based on data that suggest that FeNO added to standard management algorithms was associated with a reduced incidence of asthma exacerbations.[3,44,45] A monitoring frequency of every 2 to 3 months is recommended. The FeNO thresholds to use to adjust anti-inflammatory therapy and reduce the risk of exacerbations are not clearly established, and the same factors that can affect FeNO levels when diagnosing asthma can also affect FeNO levels when monitoring asthma.

The studies reviewed used different thresholds and strategies to monitor FeNO and adjust therapy; thus, no specific recommendations were made regarding thresholds for changing therapy. The certainty of the evidence for this recommendation overall was low with inconsistent results, particularly for severe exacerbations requiring hospitalizations,[44-48] resulting in a conditional recommendation. The effect on quality of life and asthma control did not reach the minimally important difference for the scales used,[3,5] so the primary utility of FeNO appears to be for reducing the risk of exacerbations.

Use of FeNO in Monitoring Disease Activity

The expert panel recommends against using FeNO in isolation to monitor asthma disease activity[3,5] (strong recommendation, low certainty of evidence). FeNO is not recommended for use alone to predict future exacerbations or assess exacerbation severity. FeNO levels do not correlate with standard measures of asthma symptoms or exacerbation severity. FeNO should not be used alone but rather as part of a monitoring and management strategy that includes history, clinical findings, and spirometry, as described above.

The expert panel also considered studies that used FeNO to monitor asthma control. Studies were primarily correlational and showed that FeNO levels were only weakly associated with asthma control when control was assessed using validated questionnaires.[5] The reviewed studies on using FeNO to predict asthma exacerbations had mixed results, with some studies showing it to be useful and others not.[3]

Summary of FeNO Recommendations

All of the expert panel recommendations for FeNO (Box 5) note that it should be used in conjunction with history and other testing and that absolute levels need to be interpreted in the context of comorbidities, ongoing therapy, and environmental factors that might affect the level of nitric oxide in the airway. There is concern that some individuals with asthma might have limited access to FeNO testing because of expense and availability, which might increase health-related inequality. The use of FeNO, particularly for monitoring on a regular schedule requires shared decision-making. Some individuals with asthma might find it inconvenient to undergo regular testing and find that this inconvenience and lack of benefit on asthma control and quality of life outweigh the potential benefit of reduced exacerbations.

Allergen Reduction Strategies in Asthma Management

The assessment of environmental factors associated with asthma is one of the cornerstones of asthma management from the EPR-3.[2] The EPR-3 recommended that all individuals with asthma of all severities should be assessed for exposure to allergens at home and at work, for symptoms on exposure, and for sensitization either by allergy skin testing or allergen-specific IgE (**Box 6**). The expert panel examined only the efficacy of indoor allergen strategies in mitigating critical outcomes and did not include exposure to environmental tobacco smoke, outdoor allergens, or pollutants. The expert panel examined the efficacy of single-component and multicomponent or multifaceted indoor allergen mitigation strategies and made 4 recommendations (Box 2). A single-component

mitigation strategy was defined as 1 intervention that targeted 1 specific allergen (eg, dust mite–impermeable pillow and mattress covers to mitigate dust mite exposure). A multicomponent mitigation strategy was defined as multiple interventions targeting 1 specific or multiple allergens. Integrated pest management, which consists of strategies to both reduce infestation and reduce allergen exposure, was considered by the panel as a single strategy even though it has multiple components.

In deciding whether to implement allergen mitigation strategies, the expert panel stressed that mitigation strategies needed to be allergen specific and rendered in individuals who were sensitized or symptomatic on exposure and exposed to the specific allergen. Allergen mitigation interventions are not recommended in individuals who have no history of exposure and in whom there is no evidence of sensitization and/or symptoms with exposure (conditional recommendation, low certainty of evidence). There were no distinctions in the recommendations based on asthma severity or age. Studies in children and in adults were combined in the systematic reviews and incorporated into the evidence profiles. The recommendations are thus applicable to individuals with asthma of all ages and all severities.

In general, studies that reported on mitigation interventions had numerous limitations, including inadequate characterization of the participant population, lack of blinding, small sample size, and absence of intervention standardization.[6] Baseline clinical characteristics varied considerably and may have contributed to the mixed results. Most studies either did not report on important outcomes for which validated outcome measures were available (many because of small sample size) or used nonvalidated outcome measures. Asthma symptoms were grouped together into a single category for purposes of analysis but consisted of many different outcomes, including symptom days; frequency of individual symptoms such as cough, wheeze, or dyspnea; daytime and nocturnal symptoms; and composite scores using different sets of variables. It was not possible to determine which interventions contributed to the outcomes in multicomponent interventions, and the combinations of interventions varied between studies. Overall, the benefits of the various interventions were small, and the strength of the evidence for the recommendations was low or very low, with a few exceptions as noted below.[6] However, their relatively low cost and low risk of harms (except for acaricides) and their importance in public health led the expert panel to make conditional recommendations for several of the mitigation strategies.

Single-Component Allergen Mitigation Strategies

Single-component allergen-specific interventions are not recommended (with the exception of integrated pest management) (conditional recommendation against, moderate certainty of evidence). Mitigation strategies that were reviewed for this recommendation and not recommended for use alone included use of acaricides, impermeable dust mite pillow and mattress covers, carpet removal, and high-energy particulate air (HEPA) purifiers/air filtration.

Multicomponent Allergen Mitigation Strategies

In individuals with symptoms related to exposure to specific indoor allergens, multicomponent mitigation strategies are recommended (conditional recommendation, low certainty of evidence). Evaluating the effectiveness of multicomponent mitigation strategies directed at multiple allergens was especially difficult because intervention strategies differed across studies and were targeted to different allergens.[6] For all of the interventions, the benefits were small. None of the studies demonstrated a decrease in individual measures of exacerbations (high certainty of evidence), but many of them reported improvements in asthma symptoms (moderate certainty of evidence) and in composite measures for exacerbations (low certainty of evidence). Mitigation strategies conditionally recommended by the expert panel when used in combination with other allergen-targeted interventions include dust mite–impermeable pillow and mattress covers, HEPA vacuums (for children), integrated pest management, and mold mitigation.[3]

Integrated Pest Management

The only mitigation strategy that had a small benefit when used as either a single-component mitigation intervention or as part of a multicomponent intervention was integrated pest management (conditional recommendation, low to moderate certainty of evidence). Most randomized clinical trials were conducted in children. When used in combination with other interventions, integrated pest management was associated with a decrease in a composite measure of hospitalizations, emergency department visits, and acute care visits (moderate certainty of evidence) but no change in hospitalizations (high certainty of evidence) or exacerbations leading to emergency department visits (moderate certainty of evidence).[49-57] Asthma symptoms, which were variously defined, were also reduced (low certainty of evidence), while changes in asthma control and quality of life were inconclusive.[3] Despite these limitations, the expert panel noted that pest management may have broader public health benefits. This balance between the small benefit and pest control as a public health issue influenced the conditional recommendation for integrated pest management. The public health aspects of mold mitigation also largely influenced the recommendation for mold mitigation, which was not strongly supported by the evidence.[3] Considerations regarding allergen mitigation strategies are summarized in Box 6.

Summary of Allergen Reduction Strategy Recommendations

Allergen mitigation interventions are recommended only in individuals with asthma who are both exposed to and either sensitized to or develop symptoms on exposure to specific allergens. Mitigation strategies should be allergen specific and multicomponent. Single-component allergen mitigation strategies are not recommended. The only exception is mitigation interventions for pests (cockroaches and mice), for which both single-component and multicomponent interventions are conditionally recommended.

Role of Subcutaneous and Sublingual Immunotherapy in Treatment of Allergic Asthma

Allergen immunotherapy is the administration of an aeroallergen either by subcutaneous injection (subcutaneous immunotherapy [SCIT]) or sublingually (sublingual immunotherapy [SLIT] in the form of aqueous drops or tablets) (**Box 7**). The expert panel evaluated the efficacy and safety of the use of both SCIT and SLIT for the

Box 7. Considerations for Subcutaneous and Sublingual Immunotherapy in Asthma Management

- Subcutaneous immunotherapy (SCIT) is recommended in individuals aged 5 years or older with mild to moderate persistent asthma whose asthma is definitely worsened following acute exposure on a seasonal basis (conditional recommendation, moderate certainty of evidence).
- Assessment for SCIT should be completed in a specialist's office with shared decision-making.
- Asthma should be under optimal control at the time of initiation, buildup, and maintenance of SCIT.
- Individuals with severe persistent asthma are not good candidates for SCIT because of an increased risk of adverse effects.
- SCIT should be administered under direct clinician supervision.
- SCIT is not recommended for home administration.
- Individuals undergoing SCIT should have ready availability to subcutaneous epinephrine.
- Sublingual immunotherapy is not recommended for the specific management of asthma (conditional recommendation, moderate certainty of evidence).

treatment of allergic asthma and made 2 recommendations (Box 2). Studies in children and adults were combined to increase the robustness of the reported results and it is noted when there are differences in outcomes.

The expert panel defined allergic asthma as asthma that becomes symptomatic after acute exposure to an allergen to which the individual is allergic (eg, a pet) or during a specific season (eg, in the spring, when trees and grass shed pollen, or in the fall, when ragweed pollen disperses through the air). The term *allergic asthma* is used in many clinical trials to describe a population of individuals with asthma who show evidence of allergic sensitization based on immediate hypersensitivity skin testing or in vitro serum IgE testing. Ideally, the population being studied should have both the presence of sensitization and relevant symptoms on exposure to allergens documented.

Immunotherapy (both subcutaneous and sublingual) refers to treatments used to attenuate the IgE-mediated allergic clinical response that is associated with asthma. Immunotherapy consists of therapeutic administration of exogenous aeroallergens to which a person has demonstrable sensitization with the goal of attenuating that individual's asthmatic response on subsequent exposure to these aeroallergens. Immunotherapy can be administered in 2 ways: by SCIT (in individuals aged 5 years or older) or by SLIT. The US Food and Drug Administration (FDA) has not approved the use of liquid or tablet forms of SLIT specifically for asthma. However, tablet forms have FDA approval for treatment of allergic rhinitis and conjunctivitis in individuals aged 5 years or older who have sensitization to northern grass and in individuals aged 18 years or older who have sensitization to short ragweed or dust mite mixture.

Before initiating immunotherapy, individuals with asthma need to demonstrate allergic sensitization by either (1) immediate hypersensitivity skin testing followed by an assessment 15 to 20 minutes later for a wheal-and-flare reaction to the allergens tested or (2) laboratory testing to measure the level of (aeroallergen) antigen-specific IgE antibody in a blood sample.

Subcutaneous Immunotherapy

The expert panel conditionally recommends SCIT as an adjunct treatment for individuals with mild to moderate persistent asthma (steps 2-4) who have demonstrated allergic sensitization and evidence of worsening asthma symptoms following relevant exposures (conditional recommendation, moderate certainty of evidence) (Figure and Box 2). Because none of the studies used validated asthma control instruments, the expert panel assessed the efficacy of SCIT using surrogate measures, but only when the studies used a placebo control.[3] Small benefits were found for exacerbations in 1 study (in children[58]), and mixed results were found for quality of life (2 studies demonstrated no improvement in adults[59,60]; 2 studies showed improvement in children[61,62]). Symptom diaries were used in many studies in adults and children and reported an improvement in symptoms in 59% (26 of 44 studies) of the studies with SCIT.[3] SCIT has also been found in adults to reduce quick-relief medications[63] (low certainty of evidence) and long-term medication use (moderate certainty of evidence).[60,63]

Reports of harms related to SCIT were highly variable, ranging from frequent local reactions around the injection site to systemic reactions that could include pruritus, urticaria, skin rash, rhinitis, conjunctivitis, nasal congestion, cough, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension.[8] Poorly controlled asthma is a major risk factor for fatal allergic reactions from SCIT.[3,8]

The recommendation regarding use of SCIT is conditional for several reasons. The studies available for evaluation were generally small in size, and patient populations were not well characterized in terms of race and social determinants of health. Across studies, formulations were not standardized, protocols varied, and the duration of follow-up was not uniform or standardized.[3,8]

Considerations regarding the evaluation of individuals for SCIT are listed in Box 7. It is important to emphasize that SCIT should not be administered at home but rather under direct clinical supervision and, to minimize risk, asthma should be under control at the time of initiation and during the buildup and maintenance phases of therapy.

Sublingual Immunotherapy

In individuals with persistent allergic asthma, the expert panel recommends against the use of SLIT in asthma treatment (conditional recommendation against, moderate certainty of evidence). The systematic review combined studies that used aqueous and tablet formulations to increase the sample size for many of the outcomes.[3,8] The trial designs and methodologies for studies using aqueous/drop preparations were not as rigorous or standardized as for those that used tablet formulations.

In evaluating the data from both aqueous/drop and tablet formulations combined, the evidence showed a trivial benefit for the critical outcomes, including exacerbations (with multiple different definitions), asthma control, and quality of life (moderate certainty of evidence).[64-67] For the important outcomes, the evidence suggested that SLIT leads to a reduction in the use of quick-relief medications and a decrease in ICS doses (moderate certainty of evidence).[65,67-71]

Harms as reported in the studies were difficult to evaluate. Local reactions were frequent, occurring in up to 80% of individuals receiving SLIT; however, adverse reactions also commonly occurred in those receiving placebo. The occurrence of adverse

effects did not differ by the setting of administration (home vs clinic), and the propensity for their development based on the strength of the dose administered was not consistent across studies. No episodes of anaphylaxis were reported in randomized clinical trials.[3,8]

The evidence did not support the use of SLIT specifically for the treatment of allergic asthma. Although the FDA has currently not approved SLIT tablets for asthma treatment, it has approved SLIT tablets (but not aqueous preparations) for the treatment of allergic rhinoconjunctivitis. It is therefore possible that individuals with allergic rhinoconjunctivitis who also have asthma might benefit from SLIT treatment for their asthma, and if so, this benefit is most likely related to a reduction in the use of quick-relief and/or long-term control medications.

Summary of Immunotherapy Recommendations

SCIT is conditionally recommended as an adjunct treatment to standard pharmacotherapy for individuals aged 5 years or older with mild to moderate persistent asthma who show clear evidence of a relationship between symptoms and exposure to an allergen to which the individual is sensitive. The immunotherapy recommendations call for shared decision-making between the clinician and the individual with asthma when considering this therapy.

Use of SLIT as a treatment specifically for asthma is not recommended. However, SLIT has the potential to reduce the symptoms of such comorbid conditions as allergic rhinitis and allergic conjunctivitis, and this potential improvement may be an important consideration for individuals with concurrent allergic asthma. An additional secondary benefit may be a reduction in the use of quick-relief and/or long-term control medications that the individual is receiving for their asthma treatment.

Bronchial Thermoplasty

The review of bronchial thermoplasty was a new addition in the 2020 Asthma Guideline Update. Bronchial thermoplasty is a physical modality that uses radiofrequency energy to reduce airway smooth muscle mass. The treatment is administered in 3 sessions using a proprietary delivery device as part of a bronchoscopy. The expert panel examined studies that compared bronchial thermoplasty with multicomponent medical management and that compared bronchial thermoplasty with sham bronchoscopy plus multicomponent medical management. Review of published information as of October 2018 included 3 randomized trials, all conducted by the device manufacturer, and several case reports/case series. One recommendation was made for individuals aged 18 years or older.

Based on the information reviewed, the expert panel recommends against the use of bronchial thermoplasty in adults with persistent asthma (conditional recommendation against, low certainty of evidence). This recommendation was based on several key factors. There were limited numbers of people included in the entire published literature. The critical and important outcomes of interest as defined by the expert panel for bronchial thermoplasty (exacerbations, asthma control, quality of life, and overall use of rescue medications) were either not addressed or only variably used across the available studies, resulting in uncertainty concerning the magnitude and persistence of benefits. When coupled with reported harms from the randomized trials as well as the case reports, the expert panel concluded that bronchial thermoplasty was not ready for widespread clinical use.

The participant populations included in the randomized trials were all receiving multicomponent medical therapy prior to enrollment, which included treatment with medium- to high-dose ICSs and LABAs.[72-74] In 1 study, participants could be taking a stable dose of omalizumab (the only biologic available at the time) or leukotriene inhibitors for at least 1 year prior to enrollment,[72] and 1 study included participants taking oral corticosteroids, 30 mg/d or less.[74] Individuals treated with LAMAs, environmental interventions, and newer biologic agents were not included in any of the studies. Comparator groups in the Research in Severe Asthma (RISA)[73] study (n = 32) and the Asthma Intervention Research (AIR)[74] study (n = 112) continued to receive their current medical management. In 1 study, AIR 2[72] (n = 288), the comparator group underwent a sham bronchoscopy as well as continuing their usual medical therapy.

Outcomes for all of the studies were based on 12 months of follow-up, while 2 of the studies followed up a subset of participants for 5 years. These 2 follow-up studies were the AIR Extension[74] (n = 69, of whom 45 had bronchial thermoplasty) to evaluate long-term outcomes and the AIR 2 Extension[75] (n = 162, all of whom had bronchial thermoplasty) to evaluate long-term safety. All-cause hospitalizations as well as asthma-related hospitalizations were higher in the bronchial thermoplasty groups, both at 1 year and over prolonged follow-up, in all studies.[72-74] The AIR 2 study[72] demonstrated lower rates of exacerbations requiring systemic steroids, while the RISA and AIR studies[73,74] (n = 144 people combined) showed a decrease in mild exacerbations (not requiring systemic corticosteroids). The RISA and AIR studies also demonstrated improvements in asthma control (based on Asthma Control Questionnaire[76] scores), lower rescue medication use, and fewer emergency department visits. The AIR 2 study did not demonstrate an improvement in asthma control at the population level. However, the study did show a significant difference in the percentage of participants with a minimally important change in total score of greater than or equal to 0.5 using the Asthma Quality of Life Questionnaire of 79% (intervention) compared with 64% (control). Given the variability in the results across the studies as well as other factors, the expert panel considered the overall certainty of evidence for bronchial thermoplasty to be low.

The data available on long-term outcomes are more limited than the data for 1-year outcomes. The AIR study followed 69 patients (45 receiving intervention and 24 controls) for an additional 24 months (3 years total) and did not demonstrate any differences in asthma-related events between the groups.[73] The AIR 2 trial followed 162 bronchial thermoplasty-treated participants for up to 5 years after treatment to evaluate longer-term adverse effects. This study found ongoing or new dyspnea (9.5%), chest discomfort (4.8%-8.3%), bronchial irritation (2.4%), wheezing (4.8%-8.3%), and cough (4.8%) present at the end of the 5-year study.[75] There was no comparison group in this study. In addition to hospitalization for worsening asthma, participants in the bronchial thermoplasty groups of the 3 studies were hospitalized for segmental atelectasis, lower respiratory tract infections, low forced expiratory volume in 1 second, hemoptysis, and an aspirated prosthetic tooth.[72-74]

Adverse events from case reports and small case series reported several new complications not reported in the randomized

trials, including a pseudoaneurysm of the pulmonary artery, lung abscess, inflammatory bronchial polyp, pulmonary cyst, and development of bronchiectasis.[3] There were no deaths among bronchial thermoplasty–treated patients in any of the randomized trials or case reports.

Overall improvements after bronchial thermoplasty were variable (eg, no reduction in hospitalizations across all studies, no consistent improvement in asthma control, but improved quality of life and a small decrease in exacerbations), and the harms were considered moderate. Long-term follow-up of a sufficient number of participants to fully assess clinical benefits and harms, particularly long-latency adverse effects, is lacking. Further research that includes randomized trials as well as long-term registry outcomes is desirable.

Even with a conditional recommendation against bronchial thermoplasty (ie, most patients would not want the intervention) with low certainty of evidence, FDA approval of the device means that bronchial thermoplasty is likely to continue to be used for the treatment of poorly controlled asthma. If bronchial thermoplasty is being considered, the expert panel concluded that the following issues were important as part of shared decision-making. Asthma medication should be optimized, and comorbidities addressed before moving to bronchial thermoplasty. Bronchial thermoplasty is not recommended for individuals with low lung function (forced expiratory volume in 1 second less than 50% or 60%) or life-threatening asthma (anyone who has required hospitalization in an intensive care unit, been treated with noninvasive ventilation, or been intubated for asthma in the past 5 years). Bronchial thermoplasty has not been studied in individuals younger than 18 years. Latent or delayed-onset severe complications have not been noted, but the number of individuals included in long-term follow-up is very small (<250 people at the time of the guideline). A potential candidate for bronchial thermoplasty should highly value the potential for some improvement in symptoms compared with the potential for immediate and unknown long-term adverse effects. The eFigure in the Supplement highlights the decision steps as perceived by the expert panel, including the recommendation for enrollment in a registry or clinical trial, for all individuals considering bronchial thermoplasty at this time.

Discussion

It has been 13 years since the last revision to the asthma guidelines by the National Asthma Education and Prevention Program, and in that time significant advances have occurred in the understanding of the pathophysiology of asthma and its origins. This update recommends a major change in the treatment of moderate persistent asthma in adolescents and adults with use of SMART in steps 3 and 4. The update also, for the first time, includes guidance on how to use LAMAs in adolescents and adults, the placement of FeNO testing in asthma diagnosis and monitoring, and the placement of bronchial thermoplasty (not recommended) in managing uncontrolled asthma in adults. The update also strengthens the evidence base related to immunotherapy and allergen mitigation strategies.

The 2020 Asthma Guideline Update has many strengths as well as differences with other guidelines. The topics and the subsequent key questions in the update were developed a priori, and there was input from multiple sources. The expert panel was composed of individuals representing both the asthma specialty and primary care communities. Individuals with asthma and their families provided input and preferences on which the critical outcomes were based. A strict conflict of interest policy was implemented, and individuals with conflicts were excused from all participation in the sections in which they had a conflict. Unlike many other guidelines, this update sought the input of external individuals and interest groups and received more than 500 comments from these individuals and groups that were considered in the final recommendations.

Limitations

The 2020 Asthma Guideline Update also has several limitations. First, the recommendations presented in this article are based on an initial search of the literature that concluded in March-April 2017 and was conducted by the Evidence Practice Centers of the Agency for Healthcare Research and Quality. These systematic reviews were updated through October 2018 by the expert panel and were considered in making their recommendations. A further updated search of the literature was not conducted because, in keeping with the GRADE approach that the panel used, in addition to a systematic literature search, it would have required reconvening the expert panel to review the new articles, develop new evidence profiles and evidence to decision tables, discuss the new material, and have a formal vote. This would have further delayed release of the update. While it is possible that additional studies could have influenced the recommendations, a recent review of the pharmacologic management of asthma published in 2020 is consistent with the pharmacotherapy recommendations in this update.[77] Second, a number of limitations were noted in the body of evidence that has accumulated over the past decade. A major limitation was the low frequency with which validated outcome measures were used consistently in research studies as recommended by the 2012 Asthma Outcomes Workshop.[14] Absence of these measures reduced the certainty of evidence for many of the outcomes, which altered the strength of the recommendations. Third, another major limitation was incomplete characterization of study participants. This was a particular issue in the allergen mitigation interventions in which the allergic status of participants was often not reported or included. Fourth, another limitation involved study design concerns, especially risk of bias, small sample size, and limited information about the harms and benefits of interventions if used in clinical and community settings (ie, effectiveness). Fifth, the guideline update was also limited by the focus on 6 priority topics and was not a complete revision of the guidelines. Advances in current knowledge about asthma treatment, especially asthma biologic treatment, demand an update that was not possible given the charge to the expert panel.

Conclusions

Asthma is a common disease with substantial human and economic costs globally. Although there is no cure or established means of prevention, effective treatment is available. Use of the recommendations in the 2020 Asthma Guideline Update should improve the health of individuals with asthma.

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Acquisition, analysis, or interpretation of data: All authors.
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