steps to be addressed include a further understanding of the natural history of, different host phenotype responses to, species-specific virulence characteristics, optimal treatment strategies, and environmental factors leading to the progression of NTM PD (e.g., innate host immunity, environmental exposure, and impact of other comorbidities). We may, in fact, be at the dawn of a new understanding of a much needed expansion of associated epidemiologic, pathophysiologic, diagnostic, and therapeutic possibilities of NTM PD as a credit to all those involved in the care of NTM PD, including patients, clinicians, and investigators. ■

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National Asthma Education and Prevention Program 2020 Guideline Update: Where Do We Go from Here?

The U.S. National Asthma Education and Prevention Program (NAEPP) oversaw the development of national asthma guidelines nearly 30 years ago (1). Since that time, there have been two major revisions (1997 and 2007) and one interim update (2002). In December 2020, the 2020 Focused Update to the Asthma Management Guidelines was released—the first update to the guidelines in 13 years (2).

The NAEPP 2020 update adheres to standards for trustworthy guidelines promulgated by the U.S. National Academy of Medicine, including a systematic review of the evidence that addresses specific questions, a multidisciplinary panel of experts and representatives of key affected groups, consideration of important patient subgroups and preferences, an explicit and transparent process to minimize bias

All three authors are members of the Expert Panel, and one (J.A.K.) is also a member of GINA. The views expressed in this article are their own and should not be taken as representing the views of the NAEPP Expert Panel nor GINA.

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and conflicts of interest, and ratings of both the certainty of evidence and strength of recommendations (3). An Expert Panel coordinated by the NHLBI of the NIH was first convened in July 2018 to examine six priority topics that were selected after an extensive needs assessment (4). The six topics included intermittent inhaled corticosteroids (ICS), add-on inhaled long-acting muscarinic antagonists, bronchial thermoplasty, indoor allergen mitigation strategies, immunotherapy, and use of fractional exhaled nitric oxide. No other aspects of asthma management in the NAEPP 2007 asthma guidelines (1) were considered by the Expert Panel.

The Expert Panel used systematic reviews conducted by the Evidence Practice Centers of the U.S. Agency for Healthcare Research and Quality to address key questions related to the six topics (4). Using the Grading of Recommendations, Assessment, Development, and Evaluation framework, the Expert Panel made 19 recommendations for three age groups (0–4 yr, 5–11 yr, and 12 yr or older) based on studies published through October 2018.

A conditional recommendation in the NAEPP 2020 guideline update indicates a course of action that most people with asthma would likely want but many would not and therefore warrants shared decision-making with the patient, caregiver, and clinician. A strong recommendation indicates a course of action that all or almost all people would likely choose. The Expert Panel issued draft recommendations for public comment and solicited input from federal agencies before finalizing its report in December 2020. For example, the Expert Panel for the NAEPP 2020 update concluded there was insufficient evidence to support a strong recommendation for a preferred pharmacotherapy controller in step 2 for individuals 12 years or older. By contrast, the Expert Panel offered a strong recommendation to use a single maintenance and reliever therapy with low-dose ICS-formoterol in step 3 and medium-dose ICS-formoterol in step 4 of asthma therapy in individuals 4 years or older. Because formoterol is a long-acting β_2-agonist with a rapid onset of effect and can be administered more than twice daily, ICS-formoterol can be used as a daily controller and as needed for symptom relief.

How Does the NAEPP 2020 Asthma Guideline Update Compare with Recommendations by the 2020 Global Initiative for Asthma?

The Global Initiative for Asthma (GINA) was established in 1993 by the World Health Organization and the NHLBI to promote a coordinated worldwide effort in asthma prevention and management (5). Although the Global Strategy for Asthma Management and Prevention 2020 Update (GINA 2020 report) is not a guideline, many readers of the NAEPP update are likely to ask whether the recommendations in the two documents are similar or different. The answer is yes and yes. For example, note the similarities and differences in pharmacologic step therapy recommendations for individuals age 12 years or older (Table 1).

We believe the differences are largely the result of different objectives, methods used to review evidence, and definitions. The GINA report is intended to inform a comprehensive global strategy for various aspects of diagnosis and management of mild to severe asthma, including in low- and middle-income countries. The NAEPP update offers recommendations for six priority topics. GINA updates its report annually based on a twice-yearly review of the recently published literature by asthma clinicians and researchers from diverse geographic regions in the world. The GINA report is not a guideline, so it does not adhere to methodologies recommended for guidelines. GINA advises healthcare professionals "to use their own professional judgement, and to take into account local and national regulations and guidelines" (5).

The GINA report includes five levels of progressive treatment intensification ("steps"), with step 1 therapy reserved for individuals with symptoms less than 2 times/mo. The NAEPP 2020 guideline update "pulled-through" the six-step pharmacotherapy framework used in the NAEPP 2007 asthma guidelines (1) but only made changes to some of the pharmacotherapy recommendations in the six steps in each age group. For example, in individuals 12 years or older, the Expert Panel's pharmacotherapy recommendations for the preferred controller only address steps 2–5 (Table 1). The NAEPP 2007 asthma guideline pharmacotherapy recommendations for step 1, reserved for "intermittent asthma," was not reviewed by the Expert Panel for 2020 update. GINA does not include the construct of intermittent asthma because all patients with asthma are at risk for severe exacerbations.

Given the different objectives of NAEPP and GINA, it will not be possible to harmonize all recommendations in the two documents. However, addressing some key evidence gaps related to the definition and management of mild asthma are needed. Studies are needed to determine if intermittent asthma is a clinically useful construct and whether patients with mild asthma represent a homogeneous group in terms of requirements for asthma therapy (6, 7). GINA recommends as-needed ICS-formoterol rather than as-needed inhaled short-acting β_2-agonists (SABA) in step 1 in adults based on extrapolation of evidence from corresponding step 2 studies (8). Comparative studies of as-needed ICS-formoterol versus as-needed SABA in step 1 are needed, including an assessment of harms of ICS in young children. For step 2, head-to-head comparisons of as-needed ICS-formoterol versus as-needed ICS and SABA used concomitantly are needed to determine which is the better option compared with daily low-dose ICS. More studies that identify specific patient characteristics associated with a superior response to single maintenance and reliever therapy compared with a fixed frequency of ICS–long-acting β_2-agonist with as-needed SABA are needed. Studies that include assessments of phenotype (clinical presentations) and endotype (distinct mechanistic pathways) are needed across all steps.

What Is the Role of Asthma Biologics for Severe Asthma?

The Expert Panel acknowledges that there has been remarkable progress in our understanding of the different endotypes of severe asthma and the work that has helped to establish the therapeutic use of various monoclonal antibodies ("biologics"; e.g., anti-IL5, anti-IL5 receptor-α, and anti-IL4 receptor-α) for such patients. The absence of recommendations for the use of asthma biologics in the NAEPP 2020 guideline update is a major gap, especially given the rapid pace of discoveries after the priority topics for the update were established (4). Interested readers are encouraged to review recommendations regarding the use of asthma biologics by other groups, including GINA (5) and the European Respiratory Society and American Thoracic Society (9).

Where Do We Go from Here?

The NHLBI Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network is conducting clinical trials to further refine a biomarker-driven approach to severe asthma (10). A biomarker-driven strategy may also be warranted in mild asthma (6, 7),

Table 1. Preferred Controller and Reliever Pharmacotherapy Recommendations for Individuals ⩾12 Years with Asthma in the NAEPP 2020 Guideline Update and GINA 2020 Report

	NAEPP 2020 Guideline Update	GINA 2020 Report
Step 1	Step 1 therapy not reviewed as part of NAEPP 2020 guideline update	As-needed low-dose ICS-formoterol
Step 2*	Conditional recommendation: Daily low-dose ICS and as-needed SABA or As-needed concomitant low-dose ICS and SABA	Daily low-dose ICS and as-needed SABA or As-needed low-dose ICS-formoterol
Step 3	Strong recommendation: Daily low-dose ICS-formoterol (maintenance and reliever therapy)†	Daily low-dose ICS-LABA and as-needed SABA or Daily low-dose ICS-formoterol (maintenance and reliever therapy)
Step 4	Strong recommendation: Daily medium-dose ICS-formoterol (maintenance and reliever therapy)	Daily medium-dose ICS-LABA and as-needed SABA or Daily medium-dose ICS-formoterol (maintenance and reliever therapy)
Step 5	Conditional recommendation: Daily medium- to high-dose ICS-LABA + LAMA and as-needed SABA	Daily high-dose ICS-LABA and Refer for phenotypic assessment and add-on therapy (e.g., tiotropium, anti-IgE, anti-IL5/5R, and anti-IL4R)
Step 6	Step 6 therapy not reviewed as part of NAEPP 2020 guideline update	Not applicable in GINA

Definition of abbreviations: GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = inhaled long-acting β_2-agonist; LAMA = inhaled long-acting muscarinic antagonist; NAEPP = National Asthma Education and Prevention Program; SABA = inhaled short-acting β_2-agonist.
*Use of as-needed ICS-formoterol for step 2 therapy was not reviewed by the NAEPP Expert Panel.
†Because formoterol is a LABA with a rapid onset of effect, ICS-formoterol can be used as a daily controller and as needed for symptom relief. When ICS-formoterol is used as a single inhaler, NAEPP uses the phrase "single maintenance and reliever therapy" or SMART. Except for one study that used beclomethasone, budesonide is the ICS in the studies of ICS-formoterol reviewed by the Expert Panel.

although confirmatory studies are needed. These observations suggest a future in which guidelines support a precision-medicine approach to asthma management that is based on endotype and not on age and presumed disease severity (current approach). Also, the pace of discovery is only getting faster; an update every 10–15 years is unacceptable (11). A more agile approach to developing guidelines that retains the benefits of rigor and trustworthiness is needed. We therefore advocate for a dynamic or "living" topic-driven guideline to respond more rapidly to a new body of evidence for an individual recommendation rather than the whole guideline (12). Such an approach would require a greater level of collaboration between those who develop new evidence (e.g., clinical trialists), experts in evidence synthesis (e.g., guideline methodologists), and funders who can support and plan for topic-specific updates. Importantly, an update to the NAEPP 2020 update that includes the management of severe asthma is urgently needed. ■

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