

Implementing the guidelines: What do you do when the rubber hits the road?



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The National Asthma Education and Prevention Program Coordinating Committee Expert Panel Report 4 Working Group has issued a selected update to the 2007 National Asthma Education and Prevention Program guidelines based on predetermined questions. This rostrum provides an overview of the clinically important recommendations and a guide to practical issues that clinicians may face as they implement the working group's updated guidance. It also draws attention to areas in which the recommendations differ from those of the Global Initiative for Asthma. Factors that clinicians may wish to consider as they step up therapy in the continuum of care are elaborated, especially in areas in which the update does not provide sufficient information to make a recommendation. (J Allergy Clin Immunol 2020;146:1271-4.)

Key words: Asthma, guidelines, inhaled corticosteroids, SMART, immunotherapy, exhaled nitric oxide, bronchial thermoplasty

The National Asthma Education and Prevention Program (NAEPP) Coordinating Committee Expert Panel Report 4 Working Group has issued a new set of recommendations based on specific questions addressed to the committee.¹ The members of the working group have done an outstanding job systematically evaluating the evidence and issuing carefully graded recommendations to address the questions posed. In works accompanying this one, my colleagues have reviewed each of these recommendations in detail. In addition, the working group has thoughtfully recommended areas that require further research. These

Abbreviations used

GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
LABA: Long-acting beta₂-agonist
LAMA: Long-acting muscarinic antagonist
NAEPP: National Asthma Education and Prevention Program
SABA: Short-acting beta₂-agonist
SMART: Single maintenance and reliever therapy

suggested areas of research are well considered and bear consultation by anyone interested in identifying gaps in our current understanding of the treatment and management of asthma.

Because the working group was not charged with completely updating the asthma guidelines, but rather with answering the specific questions posed, one is left with the question of how to integrate the recommendations into practice. Admirably, the working group attempted to address this issue by providing guidance for integration. To supplement this guidance, herein is presented an overview of the working group's recommendations with a discussion of implementation issues that the practicing clinician may face. In addition, attention is drawn to areas in which the NAEPP recommendations differ substantively from those of GINA (Global Initiative for Asthma) guidance regarding asthma management. The author is a member of the NAEPP Coordinating Committee but was not a member of the Expert Panel. The views expressed in this article are his own. They should not be taken as representing the views of the NAEPP Coordinating Committee.

Table I summarizes the top-line clinical recommendations that affect practice and indicates where these recommendations may differ substantively from those of GINA. Briefly, as regards fractional exhaled nitric oxide, the working group recommends fractional exhaled nitric oxide as a possible adjunct measure but not as a sole measure for diagnosis and management of asthma. In the case of indoor allergen mitigation, the working group provides clarification regarding when such measures should be undertaken and which approaches, or combinations of approaches, appear to provide benefit. Sublingual immunotherapy (SLIT) is not recommended in the treatment of asthma, and it is suggested that subcutaneous immunotherapy not be administered to patients with severe or unstable asthma. The working group suggests that the evidence base supports the use of a long-acting muscarinic antagonist (LAMA) as adjunctive therapy in adults at step 5. Lastly, the working group does not recommend the use of bronchial thermoplasty unless it is part of a registry or study.

The recommendations regarding inhaled corticosteroids (ICSs) are varied, as listed in the last section of **Table I**. They include recommendations regarding the use of short courses of ICSs, which

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TABLE I. Recommendations by the NAEPPCC EPR-4 Working Group that affect clinical care

Clinical area of interest	Selected recommendations
FENO	● FENO can be used as an adjunct measure (not as a sole diagnostic criterion) for the diagnosis and management of asthma in patients ≥ 5 y old ● FENO is NOT recommended in diagnosing asthma in patients < 5 y old ● Factors that affect FENO levels need to be considered (eg, allergen exposure and sensitivity, smoking)
Indoor allergen mitigation	● Allergen mitigation should be used only in those with allergen-induced symptoms and/or sensitization to specific indoor allergens ● Other than pest control, there is little evidence to recommend single-component interventions such as air purifiers/filtration, carpet removal, HEPA vacuums, or pet removal ● Mold removal, HEPA vacuums (for children), and impermeable mattress and pillow covers have only low to moderate certainty of efficacy in <i>appropriate</i> individuals and almost always <i>only as part of a multicomponent strategy</i> ● Pest control (cockroaches, rodents) can be used as a single modality for those with symptoms and/or sensitization with a history of exposure ● Acaricides do not appear to provide benefit
Allergen immunotherapy	● SLIT should not be used for asthma therapy* ● SCIT should not be used in patients with severe asthma ● SCIT should not be initiated or administered when patients are unstable (implying that assessments of stability should be undertaken each time SCIT is administered to patients with asthma)
LAMAs	● LAMAs can be used for some additional efficacy in addition to ICS/LABA in patients ≥ 5 y old on step 5 therapy
Bronchial thermoplasty	● Bronchial thermoplasty is not recommended for adults with persistent asthma other than as part of a registry or study
ICSs	● A short course of ICS (in addition to SABA) at the onset of respiratory illness is conditionally recommended in children ages 0-4 y with recurrent wheezing ● For patients > 4 y old <i>who are adherent to their daily ICS</i>, increasing the ICS dose in the setting of an exacerbation is NOT recommended ● PRN concomitant ICS and SABA strategy has equal preference to a daily low-dose ICS strategy in patients ≥ 12 y old with mild persistent asthma ● At steps 3 and 4, ICS/formoterol supplied as both maintenance and reliever therapy is the preferred modality for patients ≥ 5 y old, with appropriate age-related selection of the ICS dose in the formulation†

EPR-4, Expert Panel Report 4; FENO, fractional exhaled nitric oxide; HEPA, high-efficiency particulate air; NAEPPCC, National Asthma Education and Prevention Program Coordinating Committee; PRN, as needed; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

*This recommendation differs from the GINA guidelines.

†GINA does not endorse this strategy in patients 5-11 y old.

differ on the basis of age and patient adherence. The last 2 points in Table I represent a major change in recommended practice based on a redefinition of agents that can be used as reliever therapy. As a result, as-needed combination ICS/formoterol, or as-needed concomitant short-acting β_2 -agonist (SABA) with ICS, is preferred to, or placed on equal footing with, SABA alone. This approach results in a significant departure from the stepwise approach in the 2007 NAEPP guidelines. The resulting new integrated approach to escalating asthma therapy is illustrated in Fig 1. Considerations related to the use of SMART (single maintenance and reliever therapy), which is recommended in certain steps of care, are outlined in Table II. Questions that may confront clinicians as they attempt to incorporate these new recommendations into their treatment of asthma are reviewed below.

I have patients whom I have instructed to double or quadruple their ICS at the first sign of a deterioration. Their number of oral steroid bursts has decreased. Do the new recommendations mean that I should stop using this strategy? The working group recommendation not to increase the ICS dose in response to signs of deterioration applies *only in those patients who are adherent to their maintenance ICS*. This is because the evidence suggesting that this strategy may not be effective derives from controlled clinical trials where adherence to background therapy was enforced. In many cases, adherence was 80% or more in these trials. In the real world, adherence to ICS is usually poor. In the United States, only about a quarter of ICS prescriptions are renewed in a year.² In a pragmatic study by McKeever et al³ in patients older than 12 years, in which

background ICS adherence was not reinforced, quadrupling the dose of ICS in response to deterioration resulted in an almost 20% reduction in exacerbations.³ These results occurred even though more than 70% of the patients were using SMART (more about SMART below), which could have significantly blunted any effect of the dose escalation. One might consider being more cautious about using this approach in children, because one trial in children suggested that escalating ICS might result in growth delay.⁴

The working group recommends concomitant ICS and SABA for adult patients at step 2 as an alternative to continuous daily ICS. That seems to require more instruction than just telling patients to take their ICS daily. What is the advantage of the alternate approach? Studies have suggested that in patients with mild asthma at step 2, use of ICS with each dose of as-needed SABA results in asthma control (as reflected by exacerbations) that is noninferior to that achieved with routine daily ICS use, while simultaneously reducing total ICS exposure. This may be particularly attractive to patients who are concerned about ICS side effects. These studies were usually done with ICS and SABA in separate inhalers because, unfortunately, there are currently no combined ICS/SABA preparations commercially available in the United States. Thus, the working group recommended a separate inhaler strategy. Of note, several of the studies suggest that an as-needed ICS/SABA strategy may be inferior to routine daily ICS in terms of asthma control *as reflected by symptoms*. This can be a subject of shared decision making with your patient.

		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
		INTERMITTENT	PERSISTENT				
5-11 years old	DAILY CONTROLLER	None	Low-dose ICS	<u>Low-dose ICS/formoterol</u>	<u>Medium-dose ICS/formoterol</u>	High-dose ICS/LABA	High-dose ICS/LABA + OCS
	PRN RELIEVER	SABA		<u>ICS/formoterol (up to 8 puffs per day)</u>		SABA	SABA
≥12 years old	DAILY CONTROLLER	None	Preferred Low-dose ICS	Alternative None	<u>Low-dose ICS/formoterol</u>	<u>Medium-dose ICS/formoterol</u>	Medium- to high-dose ICS/LABA + LAMA
	PRN RELIEVER	SABA	Preferred SABA	Alternative ICS & SABA (concomitant)	<u>ICS/formoterol (up to 10 puffs per day)</u>		SABA

FIG 1. The chart presents the preferred stepwise approach for the management of asthma based on the NAEPP EPR-4 Working Group's update. Underlined items are areas of change from the 2007 NAEPP guidelines. *EPR-4*, Expert Panel Report 4; *OCS*, oral corticosteroid; *PRN*, as needed.

TABLE II. Considerations regarding SMART with ICS/LABA

- Formoterol is the preferred LABA due to its rapid onset of action; salmeterol has a slower onset of action and should not be used for SMART
- Although the boxed warning regarding asthma-related death has been removed from the labels of ICS/LABAs, SMART is currently an off-label use
- Studies of SMART were almost exclusively performed with budesonide/formoterol; theoretically, other ICSs could be effective as well, but they have not been studied in this manner
- NAEPP and GINA recommendations differ in several areas regarding the use of ICS/formoterol:
 - GINA does not recommend SMART for those 5-11 y old
 - GINA recommends SMART at step 5, whereas NAEPP does not
 - GINA advocates using ICS/formoterol instead of SABA as reliever therapy for *all* patients 12 y and older, including those with intermittent asthma (it does not recommend ICS/formoterol as reliever therapy in those younger than 12 y)

If concomitant ICS and SABA is a reasonable alternative for reliever therapy at step 2, why not use ICS/formoterol reliever therapy for these patients? The GINA guidelines advocate for this approach,⁵ on the basis of 2 recent studies that showed that in patients at step 2, ICS/formoterol reliever therapy is as effective as routine daily ICS in reducing exacerbations but not in reducing symptoms (an outcome similar to that cited above for concomitant ICS and SABA).^{6,7} Although ICS/formoterol reliever therapy may make sense as an alternative reliever at step 2, especially with no combination ICS/SABA products commercially available, clinicians should weigh the considerations regarding the use of ICS/long-acting beta₂-agonist (LABA) on an as-needed basis listed in [Table II](#).

The working group recommends SMART for steps 3 and 4 in children and adults. The studies were primarily performed with budesonide/formoterol. My patient's insurance will cover only mometasone/formoterol. Can ICS/LABA combinations other than budesonide/formoterol be used? SMART, in which patients use ICS/LABA as their background daily therapy and also use ICS/LABA as their reliever therapy (thus getting increased ICS every time they use their reliever), requires that the LABA have a fast onset of action. Formoterol is a LABA with a rapid onset of action; salmeterol, in contrast, has a more delayed onset of action. Thus, when using SMART, one *should not use combination products containing salmeterol*. The question of which ICS to use is less settled. Although it stands to reason that most ICSs could be effectively used in combination with

formoterol for SMART, budesonide/formoterol is by far the most studied. Still, the working group was careful to designate "ICS/formoterol" rather than "budesonide/formoterol," leaving open the possibility of using other ICSs in combination with formoterol. Once again one would want to weigh the considerations listed in [Table II](#).

My patient's insurance will not pay for 2 cannisters of the same ICS/LABA at once. Can I write a prescription for one ICS/LABA as maintenance and another as reliever? Hopefully, this reimbursement issue will be remedied over time with the adoption of the NAEPP update. The strategy outlined has never been tested. However, it stands to reason that one could use this approach as long as the reliever is a formoterol-based product and one is confident that the patient will clearly understand which inhaler to use as their reliever.

The updated and integrated NAEPP stepwise approach to therapy (Fig 1) suggests using ICS/formoterol reliever therapy at steps 3 and 4, but suggests SABA as the reliever for step 5. My patients really like using ICS/formoterol and feel that it improves their control. Won't they be confused if I ask them to go back to using SABA as their reliever if they are still symptomatic and need to move up to more intensive background therapy? The working group's decision to not recommend ICS/formoterol reliever therapy at step 5 is understandable, considering the firm guidance it received for making evidence-based recommendations. There have been no high-quality studies using ICS/formoterol as reliever in step 5 patients;

as a result, the working group did not make such a recommendation. However, this paradigm does ask clinicians, when stepping up from step 4 to step 5, to increase a patient's background therapy while, in essence, stepping down the reliever therapy. This approach may be confusing to patients (and even clinicians). In contrast, the GINA guidelines suggest that ICS/formoterol reliever therapy continue to be used in step 5.⁵ If clinicians believe it will be confusing, or inconvenient, to switch the reliever from ICS/formoterol to SABA alone, they may want to consider, in shared decision making with their patients, maintaining ICS/formoterol reliever therapy at step 5.

In parallel to the previous question, the stepwise approach (Fig 1) suggests adding a LAMA in step 5 but then does not include a LAMA in step 6. Should I take my patient off LAMA in step 6? There are no high-quality data regarding the efficacy of LAMA as part of step 6 therapy. Thus, the working group did not include LAMA in step 6. That being said, similar reasoning as discussed in the previous question applies. If the treating clinician believes it will be confusing, or the patient or clinician feels that there has been a significant benefit by the addition of a LAMA, continuation of the LAMA can be considered.

The 2019 GINA guidelines recommend using ICS/formoterol as reliever for adults with intermittent asthma, which is not consistent with the NAEPP update. What information should I use to guide decision making with my patients? The basis of GINA's recommendation in adults is extrapolated from data suggesting that even those with mild asthma can experience serious morbidity from asthma, and that ICS use reduces asthma deaths and morbidity. Large-scale trials have not been conducted. In addition, the consequences of ICS exposure to a large group of intermittent patients has not been examined. Lastly, considerations regarding as-needed use of ICS/LABA, outlined in Table II, should be weighed when determining whether to adopt such a strategy.

What about guidance on how to use biologics for my patients with severe asthma? The NAEPP guidelines, which were last comprehensively revised in 2007, have driven major changes and improvements in asthma care. The Expert Panel Report 4 working group has done an outstanding job addressing specific gaps and integrating its finding into the guidelines, but it was not charged with evaluating the role of the new biologics in asthma care. Biologics are appended in step 5 and step 6 therapy, but detailed guidance regarding their use is not provided, consonant with the charge to the group. In view of the rapid changes in the asthma evidence base and the introduction of biologic therapies, one can only hope that there will be support for frequent and comprehensive updating of the guidelines.

REFERENCES

1. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC); 2020 Focused Updates to the Asthma Management Guidelines: a Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol* 2020;146:1217-70.
2. Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015;60:455-68.
3. McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med* 2018;378:902-10.
4. Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *N Engl J Med* 2018;378:891-901.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2019. Available at: <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>. Accessed March 20, 2020.
6. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
7. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378:1877-87.