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Asthma management: How the guidelines compare

This quick guide details the similarities and differences between recommendations from the National Asthma Education and Prevention Program and the Global Initiative for Asthma.

PRACTICE RECOMMENDATIONS

› *Consider early initiation of intermittent inhaled corticosteroid (ICS)-formoterol over a short-acting beta-2 agonist for reliever therapy.* (A)

› *Start prescribing single maintenance and reliever therapy (SMART) with ICS-formoterol to reduce exacerbation rates and simplify application.* (A)

› *Consider FeNO assessment when the diagnosis of asthma remains unclear despite history and spirometry findings.* (B)

› *Consider adding a long-acting antimuscarinic agent to a medium- or high-dose ICS-LABA (long-acting beta-2 agonist) combination in uncontrolled asthma.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶

Erica S*, age 22, has intermittent asthma and presents to your clinic to discuss refills of her albuterol inhaler. Two years ago, she was hospitalized for a severe asthma exacerbation because she was unable to afford medications. Since then, her asthma has generally been well controlled, and she needs to use albuterol only 1 or 2 times per month. Ms. S says she has no morning chest tightness or nocturnal coughing, but she does experience increased wheezing and shortness of breath with activity.

What would you recommend? Would your recommendation differ if she had persistent asthma?

**The patient's name has been changed to protect her identity.*

As of 2020, more than 20 million adults and 4 million children younger than 18 years of age in the United States were living with asthma.[1] In 2019 alone, there were more than 1.8 million asthma-related emergency department visits for adults, and more than 790,000 asthma-related emergency department visits for children. Asthma caused more than 4000 deaths in the United States in 2020.[1] Given the scale of the burden of asthma, it is not surprising that approximately 60% of all asthma visits occur in primary care settings,[2] making it essential that primary care physicians stay abreast of recent developments in asthma diagnosis and management.

Since 1991, the major guidance on best practices for asthma management in the United States has been provided by the National Heart, Lung, and Blood Institute (NHLBI)'s National Asthma Education and Prevention Program (NAEPP). Its last major update on asthma was released in 2007 as the *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3).[3] Since that time, there has been significant progress in our understanding of asthma as a complex

spectrum of phenotypes, which has advanced our knowledge of pathophysiology and helped refine treatment. In contrast to the NAEPP, the Global Initiative for Asthma (GINA) has published annual updates on asthma management incorporating up-to-date information.[4] In response to the continuously evolving body of knowledge on asthma, the NAEPP Coordinating Committee Expert Panel Working Group published the *2020 Focused Updates to the Asthma Management Guidelines*.[5]

Given the vast resources available on asthma, our purpose in this article is not to provide a comprehensive review of the stepwise approach to asthma management, but instead to summarize the major points presented in the *2020 Focused Updates* and how these compare and contrast with the latest guidance from GINA.

A heterogeneous disease

Asthma is a chronic respiratory disease characterized by both variable symptoms and airflow limitation that change over time, often in response to external triggers such as exercise, allergens, and viral respiratory infections. Common symptoms include wheezing, cough, chest tightness, and shortness of breath. Despite the common symptomatology, asthma is a heterogeneous disease with several recognizable phenotypes including allergic, nonallergic, and asthma with persistent airflow limitation.

The airflow limitation in asthma occurs through both airway hyperresponsiveness to external stimuli and chronic airway inflammation. Airway constriction is regulated by nerves to the smooth muscles of the airway. Beta-2 nerve receptors have long been the target of asthma therapy with both short-acting beta-2 agonists (SABAs) as rescue treatment and long-acting beta-2 agonists (LABAs) as maintenance therapy.[3,4] However, there is increasing evidence that cholinergic nerves also have a role in airway regulation in asthma, and long-acting muscarinic antagonists (LAMAs) have recently shown benefit as add-on therapy in some types of asthma.[4-6] Inhaled corticosteroids (ICSs) have long held an important role in reducing airway inflammation, especially in the setting of allergic or eosinophilic inflammation.[3-5]

Spirometry is essential to asthma Dx—but what about FeNO?

The mainstay of asthma diagnosis is confirming both a history of variable respiratory symptoms and variable expiratory airflow limitation exhibited by spirometry. Obstruction is defined as a reduced forced expiratory volume in 1 second (FEV_1) and as a decreased ratio of FEV_1 over forced vital capacity (FVC) based on predicted values. An increase of at least 12% in FEV_1 post bronchodilator use indicates asthma for adolescents and adults.

More recently, studies have examined the role of fractional exhaled nitric oxide (FeNO) in the diagnosis of asthma. The *2020 Focused Updates* report states that FeNO may be useful when the diagnosis of asthma is uncertain using initial history, physical exam, and spirometry findings, or when spirometry cannot be performed reliably.[5] Levels of FeNO > 50 ppb make eosinophilic inflammation and treatment response to an ICS more likely. FeNO levels < 25 ppb make inflammatory asthma less likely and should prompt a search for an alternate diagnosis.[5] For patients with FeNO of 25 to 50 ppb, more detailed clinical context is needed. In contrast, the 2022 GINA updates conclude that FeNO is not yet an established diagnostic tool for asthma.[4]

A fractional exhaled nitric oxide level > 50 ppb makes eosinophilic inflammation and treatment response to an inhaled corticosteroid more likely.

Management

When to start and adjust an ICS

ICSs continue to be the primary controller treatment for patients with asthma. However, the NAEPP and GINA have provided different guidance on how to initiate step therapy (**TABLE**[3-5]). NAEPP focuses on severity classification, while GINA recommends treatment initiation based on presenting symptoms. Since both guidelines recommend early follow-up and adjustment of therapy according to level of control, this difference becomes less apparent in ongoing care.

A more fundamental difference is seen in the recommended therapies for each step (**TABLE**[3-5]). Whereas the *2020 Focused Updates* prefers a SABA as needed in step 1, GINA favors a low-dose combination of ICS-formoterol as needed. The GINA recommendation is driven by supportive evidence for

Inhaled corticosteroids can begin to reduce inflammation within days, but the full benefit may be evident only after 2 to 3 months.

early initiation of low-dose ICS in any patient with asthma for greater improvement in lung function. This also addresses concerns that overuse of as-needed SABAs may increase the risk for severe exacerbations. Evidence also indicates that the risk for asthma-related death and urgent asthma-related health care increases when a patient takes a SABA as needed as monotherapy compared with ICS therapy, even with good symptom control.[7,8]

Dosing of an ICS is based on step therapy regardless of the guideline used and is given at a total daily amount—low, medium, and high—for each age group. When initiating an ICS, consider differences between available treatment options (eg, cost, administration technique, likely patient adherence, patient preferences) and employ shared decision-making strategies. Dosing may need to be limited depending on the commercially available product, especially when used in combination with a LABA. However, as GINA emphasizes, a low-dose ICS provides the most clinical benefit. A high-dose ICS is needed by very few patients and is associated with greater risk for local and systemic adverse effects, such as adrenal suppression. With these considerations, both guidelines recommend using the lowest effective ICS dose and stepping up and down according to the patient's comfort level.

Give an ICS time to work. Although an ICS can begin to reduce inflammation within days of initiation, the full benefit may be evident only after 2 to 3 months.[4] Once the patient's asthma is well controlled for 3 months, stepping down the dose can be considered and approached carefully. Complete cessation of ICSs is associated with significantly higher risk for exacerbations. Therefore, a general recommendation is to step down an ICS by 50% or reduce ICS-LABA from twice-daily administration to once daily. Risk for exacerbation after step-down therapy is heightened if the patient has a history of exacerbation or an emergency department visit in the past 12 months, a low baseline FEV_1, or a loss of control during a dose reduction (ie, airway hyperresponsiveness and sputum eosinophilia).

Weigh the utility of FeNO measurement. The *2020 Focused Updates* also recommend considering FeNO measurement to guide treatment choice and monitoring, although this is based on overall low certainty of evidence.[5] GINA affirms the mixed evidence for FeNO, stating that while a few studies have shown significantly reduced exacerbations among children, adolescents, and pregnant women with FeNO-guided treatment, other studies have shown no significant difference in exacerbations.[4,9-15] At this time, the role for FeNO in asthma management remains inconclusive, and access to it is limited across primary care settings.

When assessing response to ICS therapy (and before stepping up therapy), consider patient adherence, inhaler technique, whether allergen exposure is persistent, and possible comorbidities. Inhaler technique can be especially challenging, as each inhaler varies in appearance and operation. Employ patient education strategies (eg, videos, demonstration, teach-back methods). If stepping up therapy is indicated, adding a LABA is recommended over increasing the ICS dose. Since asthma is variable, stepping up therapy can be tried and reassessed in 2 to 3 months.

SMART is preferred

Single maintenance and reliever therapy (SMART) with ICS-formoterol, used as needed, is the preferred therapy for steps 3 and 4 in both GINA recommendations and the *2020 Focused Updates* (TABLE[3-5]). GINA also prefers SMART for step 5. The recommended SMART combination that has been studied contains budesonide (or beclomethasone, not available in combination in the United States) for the ICS and formoterol for the LABA in a single inhaler that is used both daily for control and as needed for rescue therapy.

Other ICS-formoterol or ICS-LABA combinations can be considered for controller therapy, especially those described in the NAEPP and GINA alternative step therapy recommendations. However, SMART has been more effective than other combinations in reducing exacerbations and provides similar or better levels of control at lower average ICS doses (compared with ICS-LABA with SABA or ICS with SABA) for adolescent and adult patients.[3,4] As patients use greater amounts of ICS-formoterol during episodes of increased symptoms, this additional ICS may augment

TABLE

NAEPP and GINA 2022 recommendations for preferred step therapy in asthma for patients ≥ 12 years of age[3-5]

	NAEPP		GINA 2022	
	Severity classification guides therapy choices[a]	Preferred therapy[b]	Symptoms guide therapy choices	Preferred therapy[c]
Step 1	Intermittent	SABA as needed	Symptoms < 2 times/ mo; no risk factors for exacerbations; no exacerbations in past 12 mo	As-needed low-dose ICS-formoterol
Step 2	Mild persistent	Daily low-dose ICS, and SABA as needed OR Concomitant ICS and SABA as needed		
Step 3	Moderate persistent	Daily and as-needed low-dose ICS-formoterol (SMART)	Symptoms occur most days (eg, 4-5 d/wk); or waking at night ≥ 1x/wk	Daily and as-needed low-dose ICS-formoterol (SMART)
Step 4	Severe persistent	Daily and as-needed medium-dose ICS-formoterol (SMART)	Severely uncontrolled asthma presentation, or acute exacerbation	Daily and as-needed low-dose ICS-formoterol (SMART)
Step 5		Daily medium- to high-dose ICS-LABA + LAMA; and SABA as needed		Daily and as-needed medium-dose ICS-formoterol (SMART) + LAMA; refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLPR
Step 6		Daily high-dose ICS-LABA + oral systemic corticosteroids; and SABA as needed	N/A	N/A

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL4R, interleukin 4 receptor; IL5/5R, interleukin 5 or its receptor; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting beta-2 agonist; SMART, single maintenance and reliever therapy; TSLPR, thymic stromal lymphopoietin receptor.

[a] NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (2007).

[b] NAEPP *2020 Focused Updates to the Asthma Management Guidelines*.

[c] GINA Global strategy for asthma management and prevention (2022).

the anti-inflammatory effects. SMART may also improve adherence, especially among those who confuse multiple inhalers.

SMART is also recommended for use in children. Specifically, from the *2020 Focused Updates*, any patient ≥ 4 years of age with a severe exacerbation in the past year is a good SMART candidate. Also consider SMART before higher-dose ICS-LABA and SABA as needed. Additional benefits in this younger patient population are fewer medical visits or less systemic corticosteroid use with improved control and quality of life.

Caveats. Patients who have a difficult time recognizing symptoms may not be good candidates for SMART, due to the potential for taking higher or lower ICS doses than necessary.

SMART specifically refers to formoterol combinations that produce bronchodilation within 1 to 3 minutes.[16] For example, the SMART strategy is not recommended for patients using ICS-salmeterol as controller therapy.

Although guideline supported, SMART options are not approved by the US Food and Drug Administration for use as reliever therapy.

With the single combination inhaler, consider the dosing limits of formoterol. The maximum daily amount of formoterol for adolescents and adults is 54 µg (12 puffs) delivered with the budesonide-formoterol metered dose inhaler. When using SMART as reliever therapy, the low-dose ICS-formoterol recommendation remains. However, depending on

insurance coverage, a 1-month supply of ICS-formoterol may not be sufficient for additional reliever therapy use.

The role of LAMAs as add-on therapy

Bronchiolar smooth muscle tone is mediated by complex mechanisms that include cholinergic stimulation at muscarinic (M3) receptors.[17] LAMAs, a mainstay in the management of chronic obstructive pulmonary disease (COPD), are likely to be effective in reducing asthma exacerbations and the need for oral steroids. When patients have not achieved control at step 4 of asthma therapy, both the *2020 Focused Updates* and GINA now recommend considering a LAMA (eg, tiotropium) as add-on therapy for patients > 12 years of age already taking medium-dose ICS-LABA for modest improvements in lung function and reductions in severe exacerbations. GINA recommendations also now include a LAMA as add-on treatment for those ages 6 to 11 years, as some evidence supports the use in school-aged children.[18] It is important to note that LAMAs should not replace a LABA for treatment, as the ICS-LABA combination is likely more effective than ICS-LAMA.

The priority in addressing asthma-COPD overlap is to evaluate symptoms and determine if asthma or COPD is predominant.

Addressing asthma-COPD overlap

Asthma and COPD are frequently and frustratingly intertwined without clear demarcation. This tends to occur as patients age and chronic lung changes appear from longstanding asthma. However, it is important to distinguish between these conditions, because there are clearly delineated treatments for each that can improve outcomes.

The priority in addressing asthma-COPD overlap (ACO) is to evaluate symptoms and determine if asthma or COPD is predominant.[19] This includes establishing patient age at which symptoms began, variation and triggers of symptoms, and history of exposures to smoke/environmental respiratory toxins. Age 40 years is often used as the tipping point at which symptom onset favors a diagnosis of COPD. Serial spirometry may also be used to evaluate lung function over time and persistence of disease. If a firm diagnosis is evasive, consider a referral to a pulmonary specialist for further testing.

Choosing to use an ICS or LAMA depends on which underlying disorder is more likely. While early COPD management includes LAMA + LABA, the addition of an ICS is reserved for more severe disease. High-dose ICSs, particularly fluticasone, should be limited in COPD due to an increased risk for pneumonia. For asthma or ACO, the addition of an ICS is critical and prioritized to reduce airway inflammation and risk for exacerbations and death. While a LAMA is likely useful earlier in ACO, it is not used until step 5 of asthma therapy. Given the complexities of ACO treatment, further research is needed to provide adequate guidance.

CASE ▶

For Ms. S, you would be wise to use an ICS-formoterol combination for as-needed symptom relief. If symptoms were more persistent, you could consider recommending the ICS-formoterol inhaler as SMART therapy, with regular doses taken twice daily and extra doses taken as needed. **JFP**

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References

1. CDC. Most recent national asthma data. Accessed October 24, 2022. www.cdc.gov/asthma/most_recent_national_asthma_data.htm
2. Akinbami LJ, Santo L, Williams S, et al. Characteristics of asthma visits to physician offices in the United States: 2012–2015 National Ambulatory Medical Care Survey. *Natl Health Stat Report*. 2019;128:1-20.
3. NHLBI. National Asthma Education and Prevention Program expert panel report 3: guidelines for the diagnosis and management of asthma. NIH Publication 07-4051. 2007. Accessed October 24, 2022. www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf
4. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2022. Accessed October 24, 2022. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf
5. NHLBI. 2020 Focused updates to the asthma management guidelines. Accessed October 24, 2022. www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines
6. Lazarus SC, Krishnan JA, King TS, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. *N Engl J Med*. 2019;380:2009-2019. doi: 10.1056/NEJMoa1814917
7. Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343:332-336. doi: 10.1056/NEJM200008033430504
8. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax*. 2002;57:880-884. doi: 10.1136/thorax.57.10.880
9. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-

based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet*. 2008;372:1065-1072. doi: 10.1016/S0140-6736(08)61448-8

10. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA*. 2012;308:987-997. doi: 10.1001/2012.jama.10893
11. Garg Y, Kakria N, Katoch CDS, et al. Exhaled nitric oxide as a guiding tool for bronchial asthma: a randomised controlled trial. *Med J Armed Forces India*. 2020;76:17-22. doi: 10.1016/j.mjafi.2018.02.001
12. Honkoop PJ, Loijmans RJ, Termeer EH, et al. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: a cluster-randomized trial in primary care. *J Allergy Clin Immunol*. 2015;135:682-8.e11. doi: 10.1016/j.jaci.2014.07.016
13. Peirsman EJ, Carvelli TJ, Hage PY, et al. Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial. *Pediatr Pulmonol*. 2014;49:624-631. doi: 10.1002/ppul.22873
14. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011;378:983-990. doi: 10.1016/S0140-6736(11)60971-9
15. Shaw DE, Berry MA, Thomas M, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;176:231-237. doi: 10.1164/rccm.200610-1427OC
16. Stam J, Souren M, Zweers P. The onset of action of formoterol, a new beta 2 adrenoceptor agonist. *Int J Clin Pharmacol Ther Toxicol*. 1993;31:23-26.
17. Evgenov OV, Liang Y, Jiang Y, et al. Pulmonary pharmacology and inhaled anesthetics. In: Gropper MA, Miller RD, Evgenov O, et al, eds. *Miller's Anesthesia*. 8th ed. Elsevier; 2020:540-571.
18. Rodrigo GJ, Neffen H. Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: a systematic review. *Pediatr Allergy Immunol*. 2017;28:573-578. doi: 10.1111/pai.12759
19. Global Initiative for Asthma (GINA). Asthma, COPD, and asthma-COPD overlap syndrome (ACOS). 2015. Accessed October 24, 2022. https://goldcopd.org/wp-content/uploads/2016/04/GOLD_ACOS_2015.pdf

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28. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42:1593-1603. doi: 10.2337/dci19-0028
29. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care*. 2019;42:400-405. doi: 10.2337/dc18-1444
30. Freckmann G. Basics and use of continuous glucose monitoring (CGM) in diabetes therapy. *Journal of Laboratory Medicine*. 2020;44:71-79. doi: 10.1515/labmed-2019-0189
31. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40:1631-1640. doi: 10.2337/dc17-1600
32. Glucose monitors. Centers for Medicare & Medicaid Services. April 22, 2022. Accessed October 22, 2022. www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=33822
33. Pyl J, Dendooven E, Van Eekelen I, et al. Prevalence and prevention of contact dermatitis caused by FreeStyle Libre: a monocentric experience. *Diabetes Care*. 2020;43:918-920. doi: 10.2337/dc19-1354
34. Smith J, Bleiker T, Narang I. Cutaneous reactions to glucose sensors: a sticky problem [Abstract 677]. *Arch Dis Child*. 2021;106(suppl 1):A80.
35. MAUDE Adverse event report: Dexcom, Inc G6 Sensor. U.S. Food & Drug Administration. Updated September 30, 2022. Accessed October 21, 2022. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=11064819&pc=MDS
36. New JP, Ajjan R, Pfeiffer AFH, et al. Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). *Diabet Med*. 2015;32:609-617. doi: 10.1111/dme.12713