A Paradigm Shift for Asthma Care

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KEY TAKEAWAYS

- Asthma remains a substantial health burden, despite continued treatment advances.
- Patients with mild or moderate asthma, even those with intermittent symptoms, are at risk for severe or fatal exacerbations.
- Use of short-acting beta$_2$-agonist (SABA)-only rescue therapy is associated with an increased risk of exacerbations, beginning at about the second fill annually.
- Systemic corticosteroids have short-term and long-term adverse effects, and long-term adverse effects are driven by cumulative lifetime doses starting at 0.5 to 1.0 g.
- Expert opinion on the use of SABA only for rescue therapy differs, but recent evidence suggests that a fast-acting bronchodilator combined with inhaled corticosteroids (ICS) is more effective at reducing the risk of exacerbations than SABA alone.
- There is a window of opportunity just prior to an asthma exacerbation during which use of fast-acting bronchodilator + ICS may play a significant role in mitigating the risk of exacerbation.
- Patients may respond better to a combination inhaler of a fast-acting bronchodilator and an ICS as needed for rescue therapy or as part of a maintenance and rescue therapy paradigm, rather than attempting to use separate inhalers. However, there is currently no fixed-dose, fast-acting bronchodilator + ICS approved in the United States for as-needed use.

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DISCLOSURES

Dr. Lugogo serves on the advisory board for Amgen, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Sanofi, and Teva and has received honoraria from AstraZeneca and GSK. Dr. Skolnik serves on the advisory board or as a consultant to AstraZeneca, Teva, Lilly, Boehringer Ingelheim, Sanofi, Sanofi Pasteur, GSK, Bayer, Abbott, and Genentech, and on the speakers bureau for AstraZeneca, Boehringer Ingelheim, Lilly, GSK, and Bayer. He also receives research support from Sanofi, AstraZeneca, Boehringer Ingelheim, GSK, Bayer, and Novo Nordisk. Dr. Jiang and Austin Ulrich, PharmD, have no disclosures to report.

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INTRODUCTION

CASE SCENARIO

A 33-year-old woman with asthma presents to her primary care practitioner (PCP) in November for a routine visit. She is currently treated as a patient with mild persistent asthma and is adherent to her inhaler regimen—low-dose inhaled corticosteroids (ICS) daily—with good inhaler technique. She notes that she's feeling great and has had no trouble with her breathing recently. Her Asthma Impairment and Risk Questionnaire (AIRQ) score today is 2 (steroids in the past 12 months and emergency room visit for breathing symptoms), indicating "not well-controlled" asthma. Upon further discussion, she adds that she gets "asthma attacks" when she exercises during allergy seasons (fall and spring) and so she always uses her albuterol inhaler before jogging (5 times/week) during these times of the year.

Despite substantial advances in asthma treatment and increased availability of therapies and guidance to manage disease, asthma remains a substantial public health burden.[1] As in the case scenario, patients with mild or moderate asthma with intermittent symptoms are still at risk for adverse outcomes.[2] Primary care providers (PCPs) are essential to the optimal care of patients with asthma, as approximately 60% of patients with mild or moderate asthma are cared for by PCPs.[1,3]

In the United States, an estimated 25.1 million individuals (7.8% of the population) were living with asthma

as of 2019.[4] Of those with asthma, about 41% experience at least 1 asthma attack per year; the total number of individuals in the United States reporting an asthma attack in 2019 was ~10.3 million.[4] Approximately 1.6 million emergency department visits and 178,000 hospitalizations per year are due to asthma, with 3524 deaths nationwide in 2019.[4] Additionally, more than 7.9 million school days and about 10.9 million work days are missed yearly due to asthma in the United States, as of 2018.[5]

Asthma is a chronic, heterogeneous respiratory disease affecting adults and children of all ages[6] that is characterized by airway inflammation and symptoms that include shortness of breath, wheeze, chest tightness, and cough.[6] Symptoms and severity can change over time, often based on triggering factors such as exposure to allergens or irritants, viral infections, weather change, and exercise.[6] Although symptoms may be episodic, resolving either spontaneously or with medication use, underlying chronic airway inflammation and hyperresponsiveness may persist and vary over time to increase the risk of exacerbations.[6]

Role of PCPs in asthma care

Most patients with asthma are managed by PCPs, while some patients with severe, persistently uncontrolled asthma or in whom the asthma diagnosis is unclear are referred for specialist care.[6–8] Although the majority of patients achieve successful asthma control in primary care, there are underrecognized symptoms and risk factors, such as multiple aeroallergen sensitivities in children as well as obesity and sinus disease in adults that increase the likelihood of severe adverse outcomes in those with mild or moderate asthma.[6–9]

UNMET ASTHMA NEEDS IN PRIMARY CARE

Uncontrolled asthma

Consensus guidelines for asthma address symptom management as well as ways to decrease the risk of future exacerbations. In addition, attention is paid to lung function impairment, loss of lung function over time, and adverse effects of therapies.[6,8,10,11] Uncontrolled asthma is associated with a lower quality of life, increased rate of exacerbations, and increased healthcare utilization when compared with controlled asthma.[12,13] Improving asthma control could potentially prevent over $900 billion in direct and indirect costs over 20 years.[14,15] The Centers for Disease Control and Prevention estimated the prevalence of uncontrolled asthma at about 60% for adults in 2016 and 50% for children from 2012 to 2014, based on definitions in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report (EPR) 3 Guidelines.[10,16,17]

In a study using a national claims database of about 4.5 million patients with asthma, 3.2% were found to have severe uncontrolled asthma as defined by maintenance treatment with medium- to high-dose ICS/long-acting beta-agonist (LABA) and ≥2 claims for systemic corticosteroids (SCS) within a 12-month period.[18] Another analysis using the same database defined uncontrolled asthma as ≥3 short-acting beta$_2$-agonist (SABA) prescription fills or ≥2 SCS claims in 12 months. In this analysis, 7% of patients with severe asthma had uncontrolled disease, and 30% of patients with mild or moderate asthma had uncontrolled disease.[19]

These recent estimates reflect that the number of patients with mild or moderate asthma who are uncontrolled is about 4 times the number of patients with severe asthma who are uncontrolled (**FIGURE 1**).[18,19] Overall, approximately 81% of patients who are uncontrolled have mild or moderate asthma and 19% have severe asthma.[18] Historically, a major focus of asthma care has been on patients with severe uncontrolled asthma, but this only represents about 3% of all patients with asthma, and targeted therapies are available to treat these patients.[18,20]

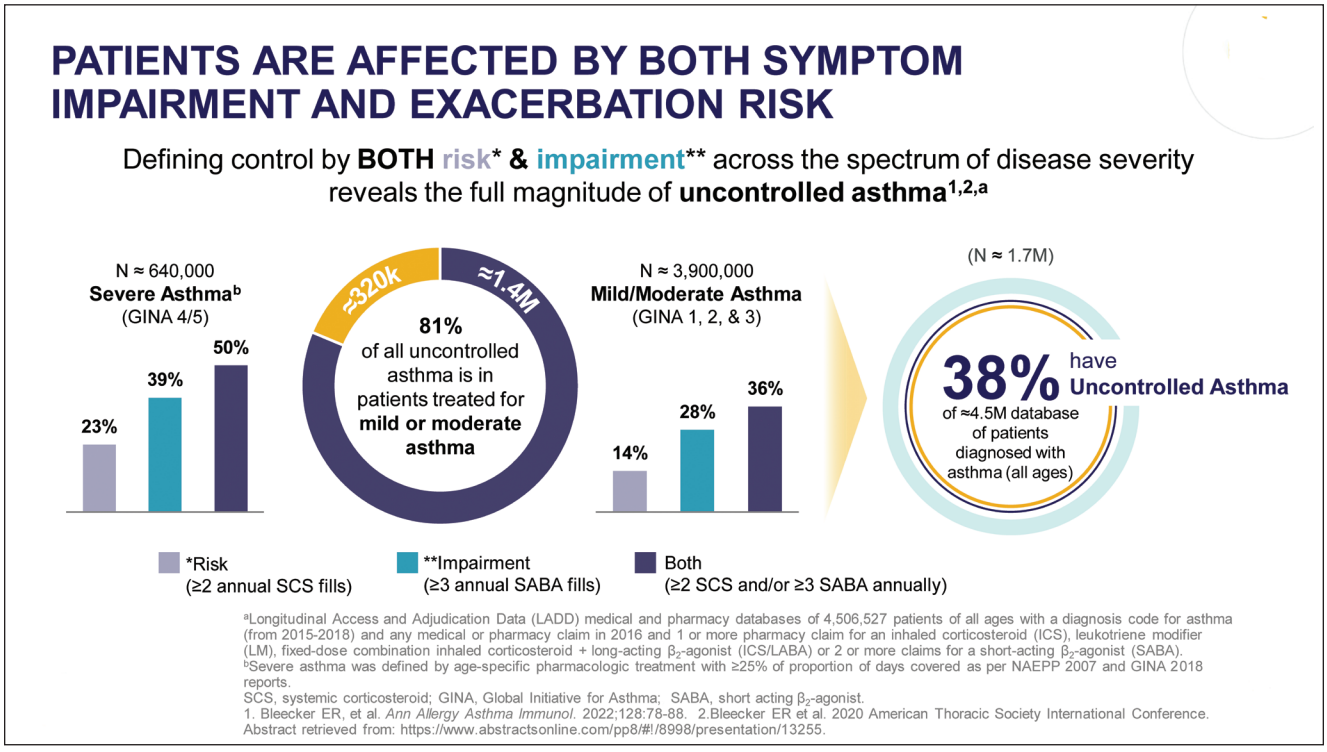
A significant challenge remains how to address patients with mild or moderate asthma who are at risk for exacerbations. It can often be difficult to identify patients with uncontrolled mild or moderate asthma due to the seasonal or intermittent nature of exacerbations; during an appointment patients may not discuss exacerbations if they are feeling well, and clinicians may think that the patient's asthma is controlled if a rescue inhaler is filled only 1 or 2 times during the prior year. To improve detection of uncontrolled mild or moderate asthma, clinicians can raise patients' awareness of what constitutes lack of control and may choose to assess asthma control and future risk of exacerbations using validated tools (see *Assessment of Asthma Control and Risk of Exacerbations* section below).[6,8]

Overuse of SCS

Use of SCS is associated with acute, as well as long-term, adverse effects. Adults aged 18 to 64 years, who received SCS for <30 days, demonstrated an increase in sepsis, venous thromboembolism, and fracture within 30 days of drug initiation.[21]

Long-term adverse effects of SCS begin to occur at approximately 0.5 g of prednisone or equivalent cumulative lifetime dose, with a clear threshold of a 1 g prednisone or equivalent cumulative dose increasing the risk of comorbidities.[22] An increased risk of osteoporosis, cataracts, pneumonia, cardiovascular diseases, cerebrovascular disease, sleep apnea, kidney impairment, depression/anxiety, type 2 diabetes, and weight gain have been associated with higher

FIGURE 1. **Percentages of patients with mild or moderate uncontrolled asthma vs severe uncontrolled asthma**



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cumulative SCS doses (**FIGURE 2**).[22] The median time period for observation and cumulative SCS dose observed was 7.4 years for the SCS group, indicating that long-term adverse effects can result from additive cumulative SCS exposure over at least 7 consecutive years.[22]

A common regimen for exacerbations is prednisone 40 to 60 mg for 5 to 10 days, for a cumulative dose of approximately 300 mg of prednisone per exacerbation. This means that patients may approach the risk threshold for long-term side effects after receiving only 2 to 3 steroid bursts.[6,10] Despite the risks of SCS, these treatments are indicated in some patients; for example, in those with severely uncontrolled asthma or in those who are experiencing an acute asthma exacerbation.[6,8]

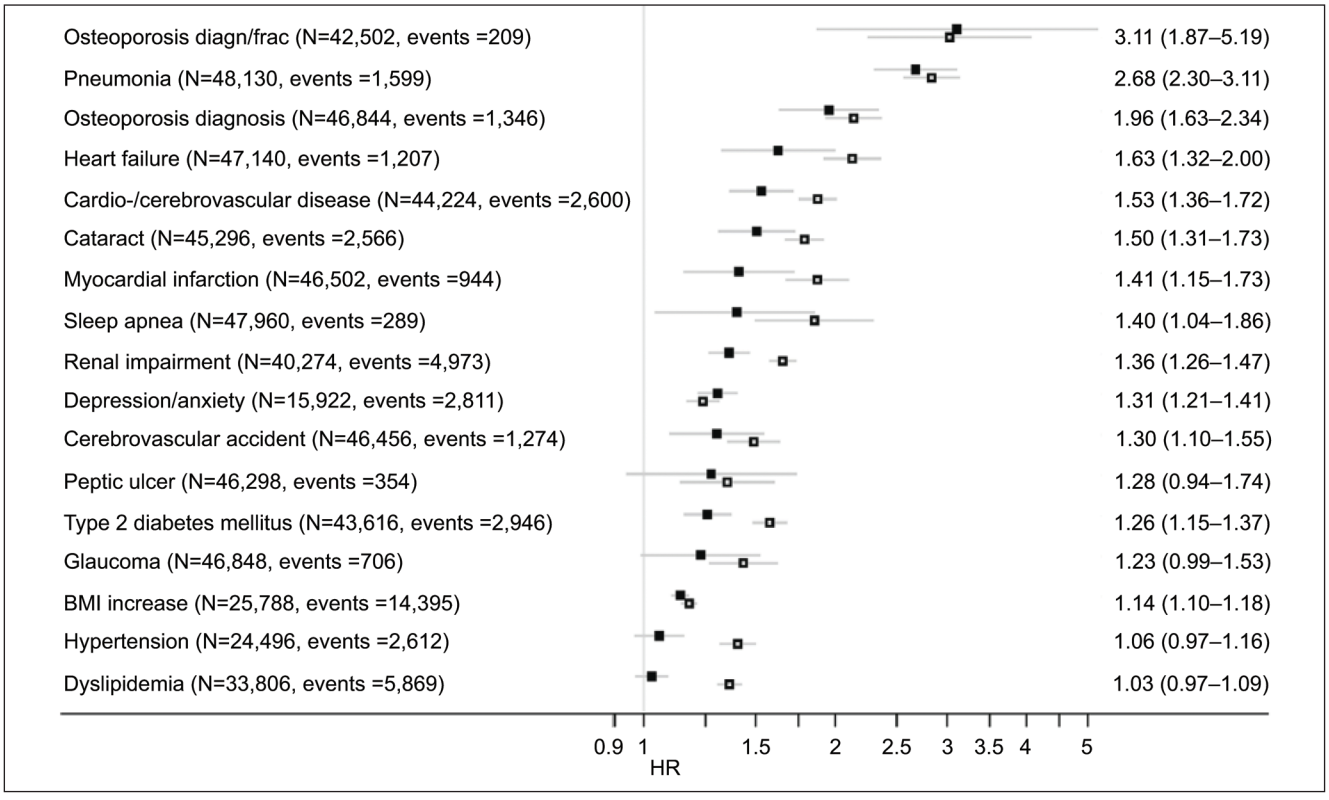
Use of SABA

Increasing SABA use is associated with an increased risk of exacerbations. A recent study demonstrated an increased risk of exacerbation associated with increasing SABA fills beginning at about the second fill, based on claims data for 135,540 patients who filled at least 1 prescription for a SABA inhaler over a 12-month period.[23] Regardless of disease severity and maintenance medication adherence, severe exacerbations occurred across cohorts, and mean SABA fills were greater for those who had exacerbations vs those who did not and for those who experienced multiple exacerbations vs those who experienced only 1 exacerbation. Moreover, as annual SABA fills increased, so did high-cost healthcare resource utilization such as emergency department and unscheduled outpatient visits and inpatient hospitalizations for asthma (**FIGURE 3**).[23]

Proposed mechanisms for increased exacerbation risk with regular or frequent use of SABA include downregulation of beta-receptors, rebound hyperresponsiveness, decreased bronchoprotection, decreased bronchodilator response, increased allergic response, and increased eosinophilic airway inflammation.[24,25] The Global Initiative for Asthma (GINA) expert report emphasizes that the risk of severe exacerbations is increased from use of SABA without concomitant ICS. SABA-only use can increase airway hyperresponsiveness and inflammation, increase exercise-induced bronchoconstriction, and reduce bronchodilator response.[6]

The International Asthma Patient Insight Research (INSPIRE) study surveyed 3415 adults with asthma being treated with ICS or ICS + LABA as maintenance therapy in 11 countries about their asthma control, medication use, and

FIGURE 2. **Hazard ratios for long-term adverse outcomes from SCS use compared with no SCS use in asthma**



Abbreviations: BMI, body mass index; HR, hazard ratio.

HR (95%) confidence interval (CI) for each adverse outcome for the SCS group vs the no SCS group.

The open squares represent unadjusted results and the closed squares, adjusted results. The adjusted HRs (95% CIs) are shown on the right.

Source: Price et al. *J Asthma Allergy*. 2018;11:193-204. Originally published by and used with permission from Dove Medical Press Ltd.[22]

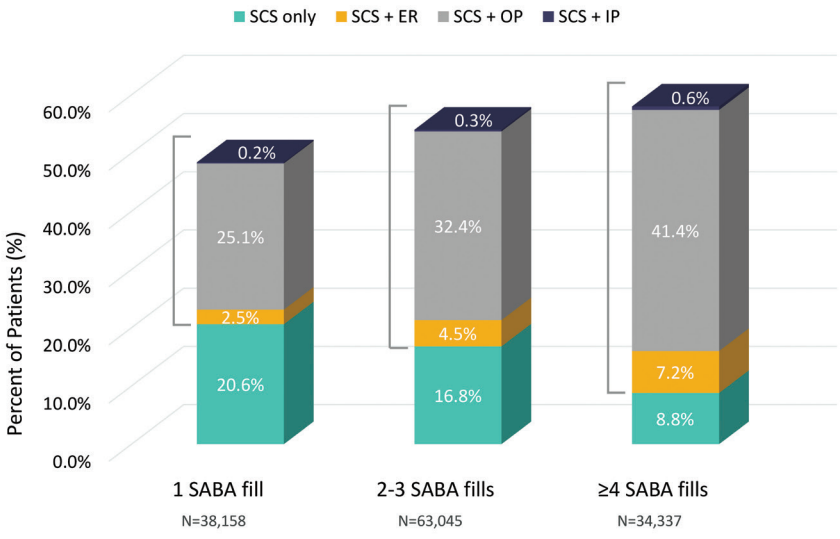
ability to recognize and self-manage worsening asthma.[26] About 74% of these patients used SABA daily despite being prescribed maintenance therapy; 38% believed there was no need to take medication daily when they felt well, and 90% of patients wanted treatments that work quickly.[26] Additionally, 51% were classified as having uncontrolled asthma based on the Asthma Control Questionnaire (ACQ).[26]

Patients often self-manage worsening asthma symptoms by increasing SABA use, aiming for immediate rescue. However, concomitant use of an as-needed fast-acting bronchodilator and ICS can both provide rapid relief and address the variability of the underlying inflammation.[27] Combination inhalers containing ICS + a fast-acting bronchodilator as maintenance and rescue therapy are more effective than higher doses of maintenance ICS and LABA.[27] This is why some have suggested using ICS alongside a fast-acting bronchodilator for treatment of escalating or increasing asthma symptoms.[27]

Budesonide-formoterol is an ICS + long-acting (and fast-acting) bronchodilator combination inhaler, and it has been studied for use as rescue and rescue and maintenance therapy for mild, moderate, and severe asthma.[28-35] Results of studies in patients aged ≥12 years showed budesonide-formoterol as rescue and as rescue and maintenance therapy reduced ICS exposure, resulted in better symptom control, and improved lung function.[28, 30-35] Collectively, trials demonstrate reductions in asthma exacerbations when budesonide-formoterol is used as needed for symptoms compared with as-needed SABA alone across all asthma severity treatment steps.[28-35] However, inhaled budesonide-formoterol in the fixed-dose combination device used in these studies is not approved and not available for rescue therapy or for maintenance and rescue therapy in the United States.

Based on US drug labeling, there is also no currently approved formulation of ICS + SABA for rescue therapy in

FIGURE 3. **Annual healthcare resource utilization associated with patients with ≥1 SCS burst**



As SABA refills increased, so did high-cost HRU

- Specific high-cost HRU services associated with non-chronic SCS use for the overall study population with any SCS bursts over a 12-month period following an index SABA fill

	1 SABA	2-3 SABA	≥4 SABA	*P*
ER	5.3%	8.4%	12.5%	< .001
OP	51.8%	60%	71.4%	< .001
IP	0.4%	0.5%	0.9%	< .001

Abbreviations: ER, emergency room; HRU, healthcare resource utilization; IP, inpatient visit (hospitalization); OP, outpatient visit.

Left: Of patients in the study population, percentage of patients in each SABA fill group with ≥1 exacerbation over a 12-month period. Right: HRU assessed only for patients in the study population with ICS exposures.

Source: Adapted from Lugogo et al. *Ann Allergy Asthma Immunol*. 2021;126(6):681-689.e1. Adaptation used with permission from AstraZeneca.

asthma in the United States. Patients can take ICS + SABA for rescue therapy in separate inhalers, based on US drug labeling, but this is not common in current practice and is cumbersome for patients because it would require the use of two inhalers each time a rescue dose is needed.

Use of as-needed ICS alongside a SABA can reduce exacerbations compared with SABA use alone. In the Person Empowered Asthma Relief (PREPARE) trial, adults with moderate-to-severe asthma were assigned randomly to patient-activated ICS along with SABA for rescue therapy and their usual maintenance therapy or SABA for rescue therapy and their usual maintenance therapy.[36] Patients who were instructed to take ICS every time they used rescue therapy had a lower annualized rate of severe exacerbations than the comparator group (0.69 vs 0.82, HR 0.85; 95% CI 0.72 to 0.999; *P* = .048). Patients in the intervention group also had better asthma control and fewer missed days of work, school, and usual activities than the comparator group.[36]

Three phase 3 trials looking at the efficacy and safety of a fixed-dose combination of a SABA and an ICS in a pressurized metered dose inhaler (albuterol-budesonide) have been completed.[37-40] The combination of albuterol and budesonide has been shown to protect against exercise-induced asthma in adolescents and adults with mild asthma compared with placebo.[40] This combination also results in better lung function compared with the individual components alone in patients with mild-to-moderate asthma.[37]

The MANDALA phase 3 randomized study evaluated the efficacy and safety of an albuterol-budesonide fixed-dose combination inhaler as rescue therapy compared with albuterol alone in 3132 patients with moderate-to-severe uncontrolled asthma. In adolescent and adult patients, the fixed-dose combination of albuterol 180 µg and budesonide 160 µg used for symptoms on top of the routine maintenance therapy demonstrated a 27% reduction in the risk of severe asthma exacerbations in a time-to-event analysis (HR, 0.73; 95% CI, 0.61 to 0.88; pre-planned efficacy analysis) compared with as-needed albuterol 180 µg.[38,39,41] Additionally, the fixed dose combination compared to albuterol alone (pre-planned efficacy analysis) demonstrated the following:

- Decrease in the annualized rate of severe asthma exacerbations (0.45 vs 0.59; rate ratio, 0.76; 95% CI 0.62 to 0.93)
- Lower mean annualized total dose of SCS (86.2 ± 262.9 mg prednisone equivalents versus 129.3 ± 657.2 mg)
- Improvement in asthma control, measured by a 24-week response on the Asthma Control Questionnaire-5 (ACQ-5; decrease of at least 0.5 points from baseline score; 66.8% vs 62.1% ; OR 1.22; 95% CI, 1.02 to 1.47)
- Improved asthma-related quality of life, as accessed

by the Asthma Quality of Life Questionnaire at week 24 (AQLQ+12, validated for persons ≥12 years of age; increase of at least 0.5 points from baseline; 51.1% vs 46.4%; OR, 1.23; 95% CI, 1.02 to 1.48).

While expert opinion differs regarding the use of SABA alone for rescue treatment in asthma, an increasing body of evidence supports administration of as-needed anti-inflammatory therapy with SABA for symptoms and to prevent exacerbations.[6,23]

MANAGING ASTHMA IN PRIMARY CARE

Use of single maintenance and reliever therapy has been recognized for years as an important part of asthma care globally.[6,8] Now, a paradigm shift in asthma care is slowly emerging for patients with asthma of mild-to-moderate severity due to the recognition that a significant proportion of asthma exacerbations occur in these patients. The shift will continue as clinicians recognize the consequences of SCS overuse and carefully consider whether rescue therapy should include an ICS, rather than SABA alone.

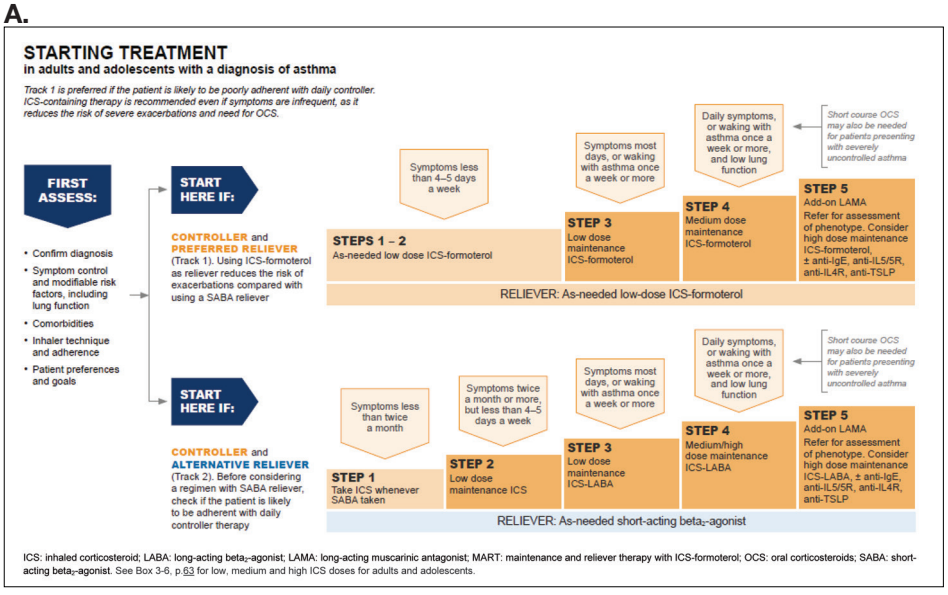
Asthma expert reports and guidelines

The most recent expert asthma reports and guideline updates are from GINA (2022) and the NAEPP (2020), respectively. The NAEPP 2020 is a focused update of the NAEPP EPR-3 guidelines (2007).[6,8,10,11]

Initial therapy. The GINA report recommends 1 of 2 "tracks" based on patient char-

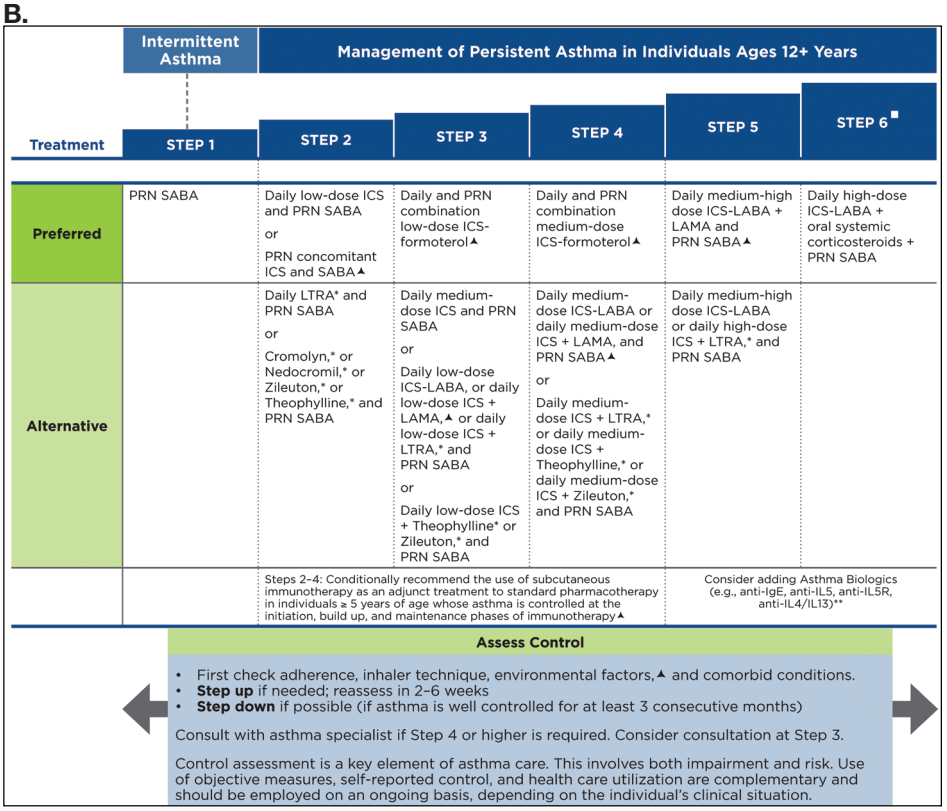
FIGURE 4. **Selecting initial controller treatment in patients aged 12 and older, according to (A) GINA reports and (B) NAEPP guidelines**

A.



Source: From GINA ©2022 Global Initiative for Asthma, reprinted with permission. Available from www.ginasthma.org.

B.



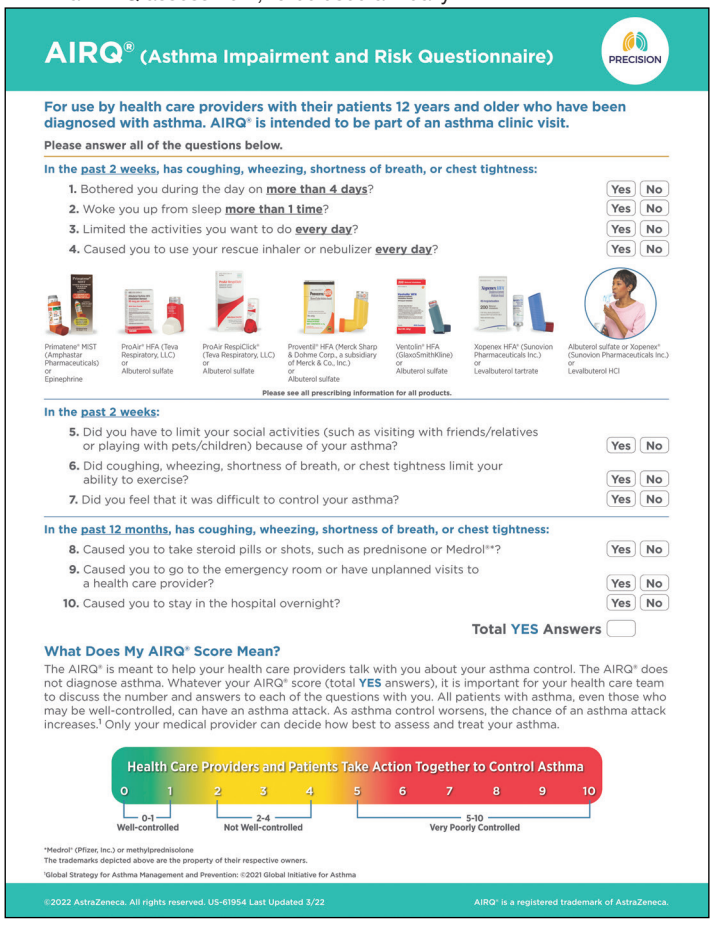
Abbreviations: LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy with ICS-formoterol; OCS, oral corticosteroids; PRN, as needed.

Note: The use of ICS-formoterol is not approved for rescue therapy or for maintenance and rescue therapy in the United States. The recommendations for ICS-formoterol are based on clinical data evaluating the use of ICS-formoterol formulations and strengths not approved and not available in the United States.

Source: Republished with permission of Elsevier, from 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group, 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), Cloutier et al. 2020;146(6):1217-1270. Permission conveyed through Copyright Clearance Center, Inc.

FIGURE 5. **The Asthma Impairment and Risk Questionnaire (AIRQ)**

A. Initial AIRQ assessment, to be used annually



AIRQ® (Asthma Impairment and Risk Questionnaire)

PRECISION

For use by health care providers with their patients 12 years and older who have been diagnosed with asthma. AIRQ® is intended to be part of an asthma clinic visit.

Please answer all of the questions below.

In the past 2 weeks, has coughing, wheezing, shortness of breath, or chest tightness:

1. Bothered you during the day on more than 4 days? Yes No
2. Woke you up from sleep more than 1 time? Yes No
3. Limited the activities you want to do every day? Yes No
4. Caused you to use your rescue inhaler or nebulizer every day? Yes No

Primatene® MIST (Amphastar Pharmaceuticals) or Epinephrine | ProAir® HFA (Teva Respiratory, LLC) or Albuterol sulfate | ProAir RespiClick® (Teva Respiratory, LLC) or Albuterol sulfate | Proventil® HFA (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.) or Albuterol sulfate | Ventolin® HFA (GlaxoSmithKline) or Albuterol sulfate | Xopenex HFA® (Sunovion Pharmaceuticals Inc.) or Levalbuterol tartrate | Albuterol sulfate or Xopenex® (Sunovion Pharmaceuticals Inc.) or Levalbuterol HCl

Please see all prescribing information for all products.

In the past 2 weeks:

5. Did you have to limit your social activities (such as visiting with friends/relatives or playing with pets/children) because of your asthma? Yes No
6. Did coughing, wheezing, shortness of breath, or chest tightness limit your ability to exercise? Yes No
7. Did you feel that it was difficult to control your asthma? Yes No

In the past 12 months, has coughing, wheezing, shortness of breath, or chest tightness:

8. Caused you to take steroid pills or shots, such as prednisone or Medrol®*? Yes No
9. Caused you to go to the emergency room or have unplanned visits to a health care provider? Yes No
10. Caused you to stay in the hospital overnight? Yes No

Total YES Answers

What Does My AIRQ® Score Mean?

The AIRQ® is meant to help your health care providers talk with you about your asthma control. The AIRQ® does not diagnose asthma. Whatever your AIRQ® score (total YES answers), it is important for your health care team to discuss the number and answers to each of the questions with you. All patients with asthma, even those who may be well-controlled, can have an asthma attack. As asthma control worsens, the chance of an asthma attack increases.† Only your medical provider can decide how best to assess and treat your asthma.

Health Care Providers and Patients Take Action Together to Control Asthma

0 1 2 3 4 5 6 7 8 9 10

0-1 Well-controlled | 2-4 Not Well-controlled | 5-10 Very Poorly Controlled

*Medrol® (Pfizer, Inc.) or methylprednisolone

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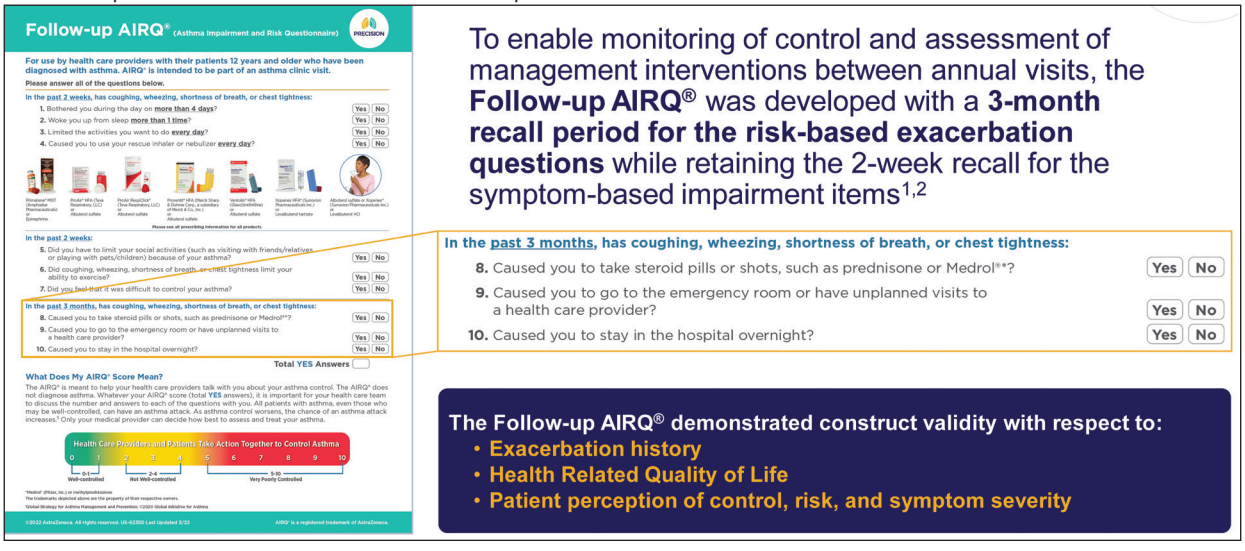
†Global Strategy for Asthma Management and Prevention: ©2021 Global Initiative for Asthma

B. Follow-up AIRQ with a 3-month recall exacerbation period



Follow-up AIRQ® (Asthma Impairment and Risk Questionnaire)

PRECISION

To enable monitoring of control and assessment of management interventions between annual visits, the **Follow-up AIRQ®** was developed with a **3-month recall period for the risk-based exacerbation questions** while retaining the 2-week recall for the symptom-based impairment items[1,2]

In the past 3 months, has coughing, wheezing, shortness of breath, or chest tightness:

8. Caused you to take steroid pills or shots, such as prednisone or Medrol®*? Yes No
9. Caused you to go to the emergency room or have unplanned visits to a health care provider? Yes No
10. Caused you to stay in the hospital overnight? Yes No

The Follow-up AIRQ® demonstrated construct validity with respect to:

- **Exacerbation history**
- **Health Related Quality of Life**
- **Patient perception of control, risk, and symptom severity**

acteristics including symptom control, adherence, and preferences and goals (**FIGURE 4**).[6] Selecting initial therapy is based on assessment of asthma severity and implementation of the corresponding level of step therapy (**FIGURE 4**).[10]

Assessment of asthma control and risk of exacerbations. Determining the degree of asthma control is essential for the ongoing management of asthma to optimize medication therapy and achieve treatment goals.[6,10] According to GINA, asthma symptom control "should be assessed at every opportunity," and NAEPP recommends periodic assessments at 1- to 6-month intervals as well as "ongoing monitoring" of asthma control.[6,10] Both expert reports acknowledge the utility of questionnaires and assessment tools to evaluate asthma control, although both also suggest a set of questions to assess control. Available asthma assessment tools include the following:

- Asthma Control Test (ACT): Scores range from 5 to 25, with higher scores indicating better control.[42] A score of 20 to 25 indicates well-controlled asthma, and the maximum clinically important difference is 3 points.[43]
- Asthma Therapy Assessment Questionnaire (ATAQ): This is a 4-question assessment, with scores ranging from 0 to 4; a higher score indicates worse asthma control.[44]
- Asthma Control Questionnaire (ACQ): This assessment includes 5 symptom questions, with SABA rescue use included in ACQ-6 and pre-bronchodilator forced expiratory volume in

1 second (FEV_1) included in ACQ-7.[6,45] Scores range from 0 to 6, with higher scores indicating worse asthma control; the total score is an average of individual items.[6]

- AIRQ: The AIRQ is a validated assessment developed in recent years to incorporate both impairment and risk assessment, the 2 key domains of asthma control (**FIGURE 5**).[46] The 7 symptom impairment questions reflect a 2-week recall period, and the 3 risk questions assess exacerbations over the prior 12 months. Scores range from 0 to 10, with a score of 0 to 1 indicating well-controlled asthma and higher scores representing worsening asthma control.[46] AIRQ control level has been found to predict risk of future exacerbations over the following 12 months.[47] Between annual visits, a follow-up version of AIRQ using the same 10 items, but with exacerbation questions having a 3-month recall period, can be used to assess disease stability and the impact of management interventions.[48]

Step therapy. Both GINA and NAEPP recommend a stepwise approach to intensifying therapy in asthma based on control.[6,8] The primary difference is that in GINA, there is a clear indication that a rescue bronchodilator should always be used with ICS for all patients aged ≥12 years, whether as formoterol + ICS or by taking ICS with each dose of SABA.[6]

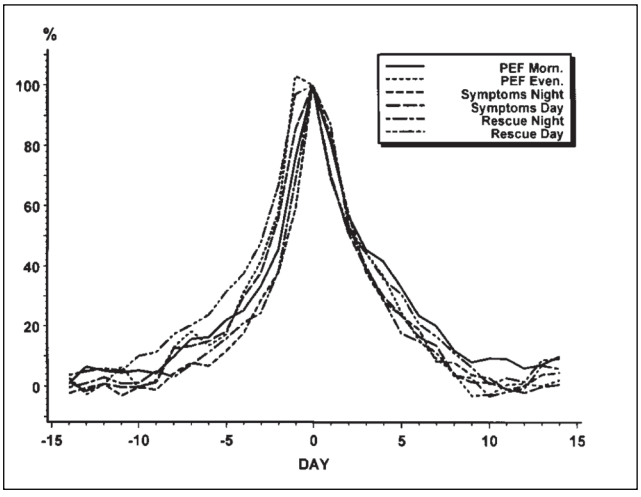
PREVENTING EXACERBATIONS: THE WINDOW OF OPPORTUNITY

Preventing exacerbations is important to decrease emergency department visits, hospitalizations, and mortality as well as for improvement in quality of life. Regular use of ICS as controller therapy leads to decreases in exacerbations, hospitalizations, and mortality, even at low doses, and the benefits of regular ICS as controller therapy are evident across asthma severity levels.[49,50] When a fast-acting bronchodilator + ICS as rescue is added to maintenance therapy, further reductions in exacerbations and improvements in asthma control and health-related quality of life have been found compared with maintenance therapy with a SABA as rescue.[30,36,41,50] Evidence is accumulating to suggest that there may be a "window of opportunity" that exists prior to an asthma exacerbation during which rescue therapy that includes ICS may prevent progression to a more severe exacerbation.[36,41,51]

Time window prior to exacerbation

Approximately 10 to 14 days prior to an exacerbation, peak expiratory flow begins to decrease, and there is an increase in symptoms and SABA utilization (**FIGURE 6**).[52-54] During this time, rising inflammation underlies the decrease in lung function that results in airway symptoms and need for SABA.[25,52] Although SABA use can bring symptomatic relief, it does not address flare-ups in airway inflammation.[25,52] This timeframe leading up to an exacerbation may represent a "window of opportunity" during which intervention with anti-inflammatory therapy can be implemented. If recognized early, prompt treatment might mitigate the rise in airway inflammation and prevent or reduce exacerbations.

FIGURE 6. **Changes in peak expiratory flow, daytime and nighttime symptoms, and rescue inhaler use during an asthma exacerbation**



Abbreviation: PEF, peak expiratory flow.

Data are standardized (Day 14 = 0%, maximum change = 100%) to allow comparison of changes with time between different endpoints. Due to the data standardization, PEF curves demonstrate an inverse relationship on the graph, where 0% indicates baseline PEF and 100% indicates worst PEF during an exacerbation. Day 0 indicates the point of exacerbation.

Source: Tattersfield AE, et al. *Am J Respir Crit Care Med*. 1999;160(2):594-599. Used with permission.

The role of ICS

Traditional teaching is that the anti-inflammatory effects of ICS take days to occur. More recent evidence supports a more rapid onset of action. ICS exert nongenomic and genomic effects that are complementary mechanisms that reduce inflammation and so may decrease the likelihood of an asthma exacerbation.[55,56] Nongenomic effects of corticosteroids have a rapid (seconds to minutes) onset of action and include decreased airway mucosal blood flow and airway edema, immune cell activity modulation, and potentiation of bronchodilator effects.[55,56] Genomic effects of corticosteroids have a delayed (4 to 24 hours) onset of action, and these effects cause increased transcription

of anti-inflammatory genes and decreased transcription of inflammatory genes.[56] Additionally, ICS decreases pro-inflammatory markers, which may offset the increase in proinflammatory markers that occurs with bronchodilators.[57,58]

Clinical evidence for ICS + fast-acting bronchodilators

The rationale for recommending a combination of ICS and fast-acting bronchodilators in the GINA expert reports is based on the increased risk of severe or fatal exacerbations as SABA is increasingly used alone, as well as evidence showing a decrease in exacerbation frequency with ICS + formoterol as controller and rescue therapy.[6,28–33,59] Several studies now provide data supporting benefits of as-needed ICS + SABA, either as a fixed-dose combination or delivered by 2 separate inhalation devices.[27,36,59,60] Thus, this indicates a clinical need for an approved ICS + SABA combination inhaler in the United States.

THE ROLE OF SHARED DECISION-MAKING AND PATIENT VOICE IN ASTHMA CARE

Incorporating patient preferences into clinical decisions is recommended for optimal asthma care.[6,10] As the focus on reducing exacerbation risk increases in patients with mild or moderate uncontrolled asthma through ICS use with rescue therapy, proper education and communication is needed to help patients understand the change in approach.

The results of the INSPIRE study highlight the tendency of patients to want treatment that seems to provide immediate relief, as well as to downplay the need for daily maintenance inhalers. The use of as-needed ICS + a fast-acting bronchodilator rescue therapy fits established patient preferences.

Revisiting the patient case scenario presented previously, the PCP might discuss with the patient how to recognize and treat pre-exacerbation symptoms due to seasonal triggers, such as rising inflammation that narrows the airways and produces shortness of breath or wheezing. The PCP could also review with the patient how to monitor her asthma with a peak flow meter as part of an asthma action plan. The action plan could also include a follow-up plan for when to speak with the PCP to optimize treatment based on clinical evidence and the patient's preferences.

SUMMARY

A large unmet need currently exists in asthma care, with over 60% of patients having uncontrolled asthma and 40% having ≥1 asthma exacerbations per year. The need for better care is not just for patients with severe asthma, as 30% to 40% of asthma exacerbations that lead to emergency care occur in patients with mild asthma. Reliance on SABA for symptom relief without using an ICS to treat underlying inflammation is associated with an increased risk of exacerbations. Adverse effects of SCS occur at much lower cumulative doses than are generally appreciated, with 500 to 1000 mg of prednisone or equivalent cumulative dose increasing the risk of comorbidities including osteoporosis, cataracts, pneumonia, and type 2 diabetes. Asthma exacerbations and need for SCS may be decreased by the use of ICS as a component of rescue therapy whenever SABA is needed. ●

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